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MANAGEMENT OF THE PRE-ALLERGIC CHILD

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I HAVE been asked to discuss the problem of the pre-allergic child. Does this mean the child who presents manifestations resembling but not clearly defined as allergic? Or, should one regard every child as potentially capable of developing allergy and consider that the management of the pre-allergic child encompasses the whole problem of the prevention of allergy? I believe the latter is indicated, and shall proceed from that standpoint.

The evidence presented in the literature shows that the placenta, the intestinal tract and the respiratory tract are permeable to unchanged or whole native proteins. Unaltered allergens may, therefore, enter the blood stream via these portals. Following the entrance of these antigens, allergic antibodies are formed and become fixed to the smooth muscle cells. When the antigen repeatedly enters the body, the child then begins to manifest true allergic episodes, either in the form of urticaria, eczema, hay fever, asthma, gastrointestinal symptoms, migraine or other neuropathies. With this brief sketch in mind, it would seem that the pre-allergic phase may be the interval which elapses before the readily recognizable patterns are established after the antigen has gained entrance into the body through the natural portals of the placenta, intestinal wall or respiratory tract, or by artificial means through injections, topical application via a break in the skin, or as a result of insect or animal bites.

The organism is provided with certain barriers which prevent the invasion of allergens into the blood stream. These barriers are the relatively impermeable skin and the mucous membranes covering the outer surfaces and body cavities and their respective tissue juices. Finally, such foreign proteins may be excreted from the body in their

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original state via the kidney. These barriers are not equally effective in all individuals, nor are they effective to a like extent at all times in the same individual, for the immaturity of the organism, pathologic states and disturbed physiology may alter them. Therefore, while individuals may be similarly exposed to antigens, it does not follow that these antigens will be similarly disposed of by the body. The alteration of any of the barriers may permit the foreign protein to enter the blood stream directly and generate specific sensitizing antibodies. Yet another factor of significance is the individual difference in capacity to form antibodies.

It may be hypothesized, therefore, that man battles continually against the invasion of foreign proteins. The difference between the normal individual, who battles successfully, and the allergic, who does not, may more largely be concerned with quantitative rather than with qualitative considerations. We must assume that quantitative applies not solely to the amount to which the individual is exposed, but to the amount of antigen which actually penetrates the tissue cells.

In the management of childhood, therefore, from the standpoint of prophylaxis, we should adopt measures aiming at the reduction of undue exposure to highly antigenic substances, particularly in vulnerable periods —roughly, intra-uterine life, infancy, illness and convalescence.

FOOD SENSITIVITY

Congenital Allergy or Intra-uterine Sensitization.—The cravings of the parturient mother and her excessive indulgence in certain foods during pregnancy account in part for some cases of food sensitivity in infancy, which to all appearances occur spontaneously from the ingestion of a new food.[5] If the mother herself is sensitive to a food, she may sensitize the infant passively to the particular allergen.

The pregnant woman, therefore, should be advised against overindulgence of any food cravings. At times, this excessive intake of a particular food may escape detection. For example, a patient may deny eating eggs in excess, and yet a careful inquiry will disclose that she is having them in the form of mayonnaise—on sandwiches and in salads—in eggnogs or other beverages, in cakes, icings, puddings, ice cream and other prepared foods. The same will hold true for milk, nuts, grains and other products which enter largely into the preparation of foods. Excessive cravings for fish, spices, nuts, fruits and vegetables are more apparent. Episodic indulgences may be as frequent a cause. A food debauch, particularly in the latter months of pregnancy, may induce sensitization in the offspring. Fad diets may have the same tendency.

A widely varied diet is helpful in meeting the problem. If the nutritional requirements of the pregnant woman make it imperative for her to have larger than usual quantities of any food element, the obstetrician may prescribe them in part in "allergenically denatured" form.

Investigations of various forms of heat-treated milks, malt and corn

sugars, cereal grains and breadstuffs by Ratner and Gruehl[6] demonstrated that animals, which had been rendered hypersensitive to certain specific food substances, can tolerate certain forms of heat-treated homologous products with little or no reaction. The studies on milk showed that the lactalbumin and lactoglobulin fractions were reduced in antigenicity when heated, i. e., evaporated or boiled. The casein is unaffected. Malt extracts, on the other hand, were highly allergenic even if heated, whereas dextri-maltose was not. With the grain foods, we found that not until the specific foods were tested could it be determined which were "allergenically denatured" and which were not. For example, certain commercially prepared dry cereals appear to be denatured, whereas certain home cooked cereals, breads and crackers are not.

From the work of Chick and Martin[1] we learn that egg white is reduced in antigenicity when heated in water, and, from clinical experience that hard boiled eggs can be tolerated by the individual who is sensitive to the albumen fraction.

Yet, foods such as nuts and fish remain highly antigenic even after cooking.

The cardinal principles to be borne in mind in avoiding intra-uterine food sensitization would be: (1) prescribe a widely varied diet, (2) give a portion of the food in "allergenically denatured" form, (3) discourage overeating, (4) warn against excessive indulgence in any single protein food and satisfaction of food cravings.

Sensitization in the Neonatal Period.—A newborn infant who receives one or several relief bottles of raw or dry milk during the first two weeks, and who then is put back on the breast entirely, may develop milk sensitization which is not evidenced until weaning is attempted. The interval between the first relief bottles and the beginning of weaning serves as the incubation period. This preliminary contact with cow's milk permits sensitization to become established. Such a situation duplicates the conditions of animal experimentation.

Sensitization may be prevented by prescribing some form of allergenically denatured milk for the relief formula, in conjunction with some denatured form of carbohydrate such as dextri-maltose.

Sensitization Following Severe Gastrointestinal Disturbances.—Hutinel[2] and others observed that after severe gastrointestinal disturbances the child may manifest sensitivity to a food for which he had complete tolerance prior to his illness. The explanation lies in the fact that the increased permeability of the intestinal wall engendered by diarrhea, for example, permits the ready entrance of unchanged protein into the blood stream.

It is important, therefore, during treatment and convalescent care of severe intestinal disturbances, such as diarrhea, dysentery, and typhoid

fever, (1) to give "allergenically denatured" foods, (2) to give a varied diet, and (3) to avoid new foods and raw or lightly cooked foods.

Sensitization During Convalescence from Disease.—The increased permeability of the intestinal wall, characteristic of severe intestinal disturbances, also occurs during convalescence from other diseases, and following surgical operations, where loss of weight and wasting are evident. Foods that are not cooked, for example, eggnogs, fruit whips and raw milk, are all potential sensitizing agents. From what has been pointed out, the wise course to follow is the same as that indicated in intestinal cases, rather than the generally prescribed diet which at present consists largely of raw and lightly cooked foods.

Sensitization Resulting from Excesses in Diet and Unusual Foods.—Experience shows that sensitization may occur to common foods taken in excess, milk, egg and wheat being the chief offenders. Seasonal foods that are eaten at infrequent intervals and in great quantities, e.g., shell food, berries, nuts and other seasonal fruits and vegetables, are also potential sensitizers.

The practice of overfeeding infants and the present vogue for introducing many new foods very early in infancy fall into this category.

Fad diets are usually composed of a limited number of foods, and very often raw foods. It is reasonable to assume that they may lead to food sensitization.[7] The danger of introducing an unusual substance is exemplified in the somewhat bizarre and extreme case reported by Stuart and Farnham,[11] of an individual whose sensitivity to fish dated from the drinking of a can of glue on a bet.

The prophylactic measures in all these instances are obvious.

INHALANT SENSITIVITY

Dust sensitivity is due chiefly to exposure to specific dust allergens. Early infancy and prolonged confinement to the sickroom are particularly vulnerable periods.

In developing a prophylactic program, attention is first focused on the nursery. It should be furnished very simply, with no hangings and no heavy rugs. Everything in it should be washable. Feather pillows, comfortables, overstuffed furniture, which produce much dust, should be eliminated altogether or at least reduced to a minimum. A mattress and pillow stuffed with a good quality of hair is preferable, although good cotton linter and feather stuffed ones that are securely covered with an impervious textile may be safe. Many substitute stuffings, such as fibreglas, rubber foam, et cetera, are being developed and may prove effective.

Heavy silk and woolen materials that shed easily must be avoided, not only in the immediate environment, but also as clothes.

Furniture that gives off dust, even in other rooms, should be carefully covered with down-proof material.

Infants and young children should not be permitted to sleep with pets or stuffed toys.

It may be instructive to cite examples of contact with dust allergens. There is the striking instance of the child who from early infancy slept on a mattress containing cattle hair, and in early childhood had a hobby-horse covered with cattle hair. Elimination of the hobbyhorse and mattress relieved his asthma.

Another child developed his first attack of asthma after lobar pneumonia at the age of two years. I discovered that he had been sensitized to the rabbit hair in pillows in the home of his grandmother, with whom he lived for a period, and to which he returned to convalesce after the pneumonia. The father was employed in a felt hat factory and subsequent attacks were traced to the rabbit fur dust adhering to the father's clothes.

An infant, whose bedroom window faced directly on a stable, became so profoundly sensitized to horse dander, and as a consequence to the related protein in horse serum, that anaphylactic shock resulted from a first small injection of horse serum.

Recently, I met a young man whose case might also be cited as a controlled experiment. He was the son of the proprietor of an inn situated directly on the shore. At the age of twelve, he became the proud possessor of a pony. The father presented each of his three sons with one on the promise that they would take care of the animals. For three months this boy currycombed and groomed his pet. Then he went off to school, while his brothers stayed at home. When he returned, after a period of eight months, he discovered that every time he went to the stable, he had a most uncomfortable choking sensation. One day a guest saw him in one of his "spells," which he recognized as asthma. Upon investigation, he proved to be skin sensitive to horse dander, and he has been clear of difficulties since he has avoided contact with horses. There was no history of allergy on either side of the family, and it is interesting that the two brothers who remained at home continuously did not develop any difficulties.

Pollinosis may result from undue exposure to pollens. Piness and Miller[4] described the interesting case of a group of city dwellers who were transferred to a mountain community, where they were exposed to unusual amount of pollens, some of which were foreign to their previous environment. As time went on, a large number developed hay fever. Family history seemed to play a minor role. Other cases, less striking perhaps, have been cited in the literature, showing the relationship of undue exposure to pollens and the consequent development of hay fever.

Such cases are very like our animal inhalation experiments.[8] Animals, exposed to a dust-laden atmosphere for a short period, are difficult to sensitize. As the length of the exposure is increased, a greater number of animals are sensitized. An instructive experiment was one in which

we studied a female guinea pig and her four offspring. Three of the latter were exposed to an antigenic dust. After an interval of several weeks, the mother and the entire litter were placed in the dust chamber. The three which had been previously exposed showed signs of experimental asthma, whereas the two that had no previous contact remained unaffected.

From the standpoint of prophylaxis, the seashore or other sections of the country that are relatively free from pollen may be more advisable for vacation purposes for the infant and young child.

Insecticides which contain pyrethrum should be avoided since this ingredient appears to be a potent allergen, closely related biologically to ragweed pollen.

DRUG ALLERGY

Although hypersensitiveness is primarily due to protein substances, it has been shown that substances other than protein can induce specific hypersensitivity. Drugs in themselves are not antigenic, but may form antigenic conjugates in combination with proteins of the animal body, called *haptens* by Landsteiner,[8] which are capable of inducing sensitization.

Striking instances of drug sensitivity have been reported, especially when used in large doses and in recurrent conditions. The phenolphthalein group of cathartics are notorious for their production of fixed drug eruptions. The pyramidon and allonal group have been assumed to be causative agents in the development of agranulocytosis. The indiscriminate use of external medicaments for the skin and mucous membranes has resulted in specific sensitivity.

Today, the sulfa combinations and antibiotics such as penicillin, streptomycin, have sprung into prominence and are being used to an alarming degree. Many reports have already appeared in the literature indicating that allergy may result from their repeated use. In my book[9] I made a plea that their indiscriminate use should be curtailed. Sensitivities arising from their use may account for much of the allergy of the future.

Infants who react severely to a drug given for the first time may possibly have been sensitized *in utero*. Caution should therefore be observed in the administration of drugs to pregnant women and nursing mothers.

BACTERIAL ALLERGY

Our knowledge of bacterial allergy is comparatively scant, and it is therefore difficult to say how it may be successfully diagnosed and differentiated from the disease with which it is associated.

According to Zinsser,[12] it seems reasonably clear that in bacterial allergy we are dealing with the sensitization of the body by autolytically liberated antigenic substances which are absorbed from any focus in which bacteria react with inflammatory tissues, and as a result of which the body

is subsequently rendered sensitive to contact with these same autolytic products, whether they are liberated and absorbed from a chronically existent focus or from an identical infection subsequently acquired.

It is true that the allergic phenomenon results from a mild, nonprogressive, and transitory irritation of sensitized tissue. It can, however, hardly be questioned that a body which is allergic to a given bacterial antigen is vulnerable to a degree that may lead to serious pathologic change, such as inflammation, extensive edema, hemorrhagic transudation, and even necrosis. The reactions are, as a rule, explosive in nature.

The repeated common cold or coryza may yet be proved to be attributable to an allergic basis. Zinsser described the simple experiment of taking a hot bath and then exposing oneself to cold air until an uncomfortable chilly feeling is experienced. Such a procedure usually results within twelve hours in the early signs of a cold which runs its ordinary course. According to Zinsser, this definite train of events excludes infection from without and can be explained only by one of two alternatives—either a direct invasion by bacteria previously present on a mucous membrane in which the capillary disturbances due to the chilling have permitted penetration; or, by an allergic reaction of a sensitive mucous membrane to the bacterial antigens present in the nose when the communication between tissues and surface is established by the capillary permeability resulting from the chilling. It is more than likely that human beings are all sensitive to one or more of the organisms present in their respiratory tracts and that the degree of this sensitiveness fluctuates according to the recently existing local flora. The noticeable similarity of the early stages of such reactions to the allergic conditions mentioned above, the speed of onset, and the almost bacteria-free condition of the early exudate in many cases favor an allergic mechanism.

After the allergic reaction has been provoked, it is only natural that a secondary bacterial inflammatory process should supervene. It is for this reason that all infectious processes in early infancy and childhood should be meticulously treated. The prevention of recurrent episodes should materially reduce the severity of the infections. The proper hygienic and dietary measures and the judicious use of vaccines are all efficacious in the prevention of bacterial allergy.

That so destructive a disease as rheumatism may have for its underlying mechanism an allergic reaction to some form of hemolyzing streptococcus is indicated by a great deal of experimental evidence. It is needless to say that the most important work to be done in rheumatism is preventive.

Scarlet fever, tuberculosis, and pneumonia need only be mentioned here, for there is much which is yet to be accomplished in the allergic aspects of these diseases.

It has been pointed out that certain diseases, such as pertussis, pneu-

monia, measles and scarlet fever, often antedate asthma. Whether any direct relationship exists between these diseases and the subsequent allergy is difficult to determine. An increase in membrane permeability, permitting a more ready entrance of sensitizing substances, may be an underlying factor.

Whatever the basis, it would seem reasonable to suggest that all available immunizing measures against infectious diseases should be more generally employed in childhood.

SERUM HYPERSENSITIVITY

Serum hypersensitivity may result from several causes. We have shown experimentally that an animal sensitized through the inhalation of horse dander may succumb to a primary injection of horse serum. Similarly, a child with horse dander or rabbit hair sensitivity may die in anaphylaxis or have a profound anaphylactic reaction when given a first injection of antiserum.[10]

Sensitivity to serum may result from horse or rabbit meat ingestion. This is less common in America than it is in Europe.

Sensitization to serum may result from repeated injections of antisera.

In order to prevent serum accidents, it is essential for the physician to test every child for serum sensitivity before administering an antiserum. If the child gives a systemic reaction, manifested by urticaria, or dyspnea, he should, as a rule, not be given the serum. If it is mandatory, it should be given slowly in small doses, subcutaneously, or by slow intravenous injection, diluted with saline, concomitantly with adrenaline and atropine.

Too often, tetanus antitoxin is given without adequate provocation. It is better to treat a superficial wound surgically than to resort immediately to tetanus antitoxin. No fixed rules can be laid down, and one must be guided by the circumstances in the individual case.

In the prophylaxis of diphtheria and tetanus, toxoid is almost universally used today, which has materially reduced the incidence of serum sensitivity. It is essential that every allergic child be properly immunized, with booster doses given at subsequent intervals. The actual prevention of serum sensitivity can best be accomplished by diminishing excessive contact with horses and rabbits, by desensitization of patients sensitive to animal dander, and by a reduction in the indiscriminate use of antisera in childhood meningitis, suspected diphtheria and tetanus.

SUMMARY AND CONCLUSIONS

1. Allergy may develop in children whether born into allergic or nonallergic families, because all individuals are potentially capable of developing sensitivities.

2. Antigens or antibodies may be transmitted to the fetus through the placenta. Unaltered proteins may pass through the walls of the digestive

tract or the upper respiratory tract. Unaltered allergens may enter the blood stream by way of the skin or by parenteral injection.

3. The acquisition of hypersensitiveness depends upon: (a) constitutional or other factors peculiar to the individual, (b) the nature of the exciting substances, (c) the amount of antigen to which the individual is exposed, (d) the amount of native antigen which actually invades the blood stream, and (e) the intervals at which such exposures occur. In my estimation quantitative factors play a larger role than do qualitative ones.

4. Intra-uterine life, infancy, illness and convalescence constitute vulnerable periods, during which the individual must be protected especially from undue exposure to highly antigenic substances.

5. Much can be accomplished prophylactically in the management of the pre-allergic child by the adoption of measures which aim to prevent the inception of food, dust, drug, serum and bacterial sensitivity through the regulation of the diet, the management of the environment, the control of drug and serum therapy, and the reduction of recurrent invasions of pathogenic agents.

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REFERENCES

1. Chick, H., and Martin, C. J.: On the "heat coagulation" of proteins. J. Physiol., 40:404, 1910.
2. Hutinel, Victor H.: Intolerance pour le lait et anaphylaxie chez les nourrissons. Clinique, Paris, 3:227, 1908.
3. Landsteiner, K.: The Specificity of Serological Reactions. Springfield, Ill.: Charles C. Thomas, 1936.
4. Piness, G., and Miller, H.: Unusual opportunity to make allergic study of entire community with etiology and results of treatment. J. Allergy, 1:117, 1930.
5. Ratner, B.: A possible causal factor of food allergy in certain infants. Am. J. Dis. Child., 36:277, 1928.
6. Ratner, B., and Gruehl, H. L.: Anaphylactogenic properties of milk. Am. J. Dis. Child., 49:287, 1935.
6a. Ratner, B., and Gruehl, H. L.: Anaphylactogenic properties of malted sugars and corn syrup. Am. J. Dis. Child., 49:307, 1935.
6b. Ratner, B., and Gruehl, H. L.: Anaphylactogenic properties of certain cereal foods and breadstuffs. Am. J. Dis. Child., 57:739, 1939.
7. Ratner, B., and Gruehl, H. L.: Passage of native proteins through the normal gastrointestinal wall. J. Clin. Investigation, 13:517, 1934.
8. Ratner, B.: Experimental Asthma. Am. J. Dis. Child., 58:1, 1939.
9. Ratner, B.: Allergy, Anaphylaxis and Immunotherapy. Baltimore: Williams & Wilkins, 1943.
10. Ratner, B.: A possible explanation for horse serum anaphylaxis in man. J.A.M.A., 94:2046, 1930.
11. Stuart, H. C., and Farnham, M.: Acquisition and loss of hypersensitiveness in early life. Am. J. Dis. Child., 32:341, 1926.
12. Zinsser, H.: Significance of bacterial allergy in infectious diseases. Bull. New York Acad. Med., 4:351, 1928.

THE TOPICAL APPLICATION OF THEPHORIN IN PRURITIC DERMATOSES

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THE specific treatment of allergic dermatoses is, unfortunately, disappointing, and there have been but few notable advances in recent years. Specific hyposensitizing measures have not proved of much value in contact dermatitis due to poison ivy or other plants, atopic dermatitis, urticaria and dermatoses produced by drugs and physical agents. It is not surprising, therefore, that efforts have been made to treat various allergic dermatoses by nonspecific means. Unfortunately, in most cases the older non-specific remedies such as histamine, histamine protein conjugate (Hapamine), and histaminase all proved about as disappointing as the specific measures.

In 1936 Dragstedt and Mead[2] reported experiments indicating that many of the major symptoms of anaphylactic shock could be accounted for by the quantity of active histamine present in the blood and lymph at the time the reaction occurred. These and other experiments have stimulated various workers to develop drugs which are capable of diminishing or preventing several of the pharmacologic effects of histamine.

Fourneau[4] and his French associates developed the first of the so-called antihistaminics or histamine antagonists and since then, as is well known, numerous compounds have been evolved many of which have a clinical effectiveness without prohibitive side effects. These agents, when administered orally, are undoubtedly of value in certain allergic dermatoses such as urticaria (both acute and chronic), urticarial drug eruptions, some physical allergies, some cases of pruritus ani and vulvae, and in a few cases of atopic and contact dermatitis. The fact that the oral administration of the histamine antagonists is of value in the treatment of allergic dermatoses led to the hope that the topical application of these drugs might be of additional help.

In 1947, Mayer[8] reported experimental epidermal sensitization to paraphenylenediamine in guinea pigs. He showed that greater protection to subsequent applications of the chemical could be obtained by the local application of 5 per cent triplennamine hydrochloride (Pyribenzamine) in sesame oil than by the parenteral injection of the same drug. He theorized that this was brought about because there was a higher concentration of the drug at the test site plus the influence of a possible effect of local anesthesia.

In 1947, Feinberg and Bernstein[3] used 2 per cent Pyribenzamine ointment in thirty-three cases of atopic dermatitis of varied extent, chronicity and severity. All of the patients were studied for allergic factors and

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the majority disclosed definite cutaneous reactions and observations which indicated a relationship between the eczema and specific allergenic causes. They reported that twenty-four of the patients noted consistent relief from the use of the ointment. In most instances the greatest relief was obtained in patients whose lesions were localized to small areas. A combination of oral and topical medication seemed most beneficial although in a few instances the local or oral treatment was the only one effective. In a few patients the ointment was irritating, especially those in which the lesions were acutely inflamed. The Pyribenzamine ointment gave symptomatic relief to eight of nine patients with pruritus ani. In two patients with contact dermatitis of the eyelids, two of dermatitis of the arms of unknown nature, and one of dermatitis of the legs of unknown cause, improvement in the itching was obtained. In a patient with urticaria, the pruritus caused by the individual lesion was relieved by the application of the ointment while in four other cases of dermatitis no benefit was obtained. Sulzberger, Baer, G. Rubin and others[10] working with Pyribenzamine cream at the New York Skin and Cancer Unit obtained results which were somewhat in contrast with those of Feinberg and Bernstein. Sulzberger and his colleagues found that the only dermatitis in which local application of Pyribenzamine cream was of antipruritic value in a significant proportion of cases was lichen chronicus circumscriptus (circumscribed neurodermatitis). Local application of the antihistaminic agent was not only of no value but even aggravated the lesions of atopic dermatitis (disseminated neurodermatitis) in most of their cases.

Friedlaender and Feinberg[5] showed in 1946 that the local application of a solution of beta-dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) to a scratch on the skin of an allergic person inhibited the normal whealing from histamine or that from an antigen such as ragweed. These workers also showed that solutions of histamine antagonists could penetrate the unbroken skin. This was demonstrated by applying the antihistaminic to an area of dermographic skin and then stroking the part and the contiguous untreated skin. Whealing took place only at the untreated areas, skipping the treated site.

Leavitt and Code[6] experimentally demonstrated the anesthetic action of Benadryl in the skin of human beings. The drug was injected intracutaneously on the flexor surface of the forearm and was found to produce more intense anesthesia than injections of procaine of comparable strength. There was no apparent correlation between the anesthetic effect and the antihistaminic activity.

In 1947, Perry[9] reported on the local use of Benadryl ointment. Two per cent Benadryl was incorporated in a water-soluble ointment base and applied to the skin. The effect on the wheals and erythema produced by intradermal injections of 0.1 c.c. of 1:100,000 dilution of freshly prepared histamine phosphate was studied. He found that there was no significant

difference in the diameter of intensity of the erythema and the wheal produced by histamine, with or without the ointment. The same preparation was applied topically in twenty-two patients with various pruritic dermatoses. There was no supplemental therapy. Six patients had moderate and two had excellent relief of the pruritus. Four of these, however, had the same degree of relief from the ointment base alone. Perry believed that his studies indicated that Benadryl in the preparations studied was probably not absorbed in sufficient quantities to produce a clinical effect following local application and that it had no significant antipruritic effect.

Thenylpyramine hydrochloride is also available for topical application (cream Histadyl Hydrochloride, Lilly). The drug is incorporated in a greaseless ointment base in a concentration of 2 per cent and is claimed to be of value in allergic contact dermatoses and for local analgesic action in pruritus ani and vulvae. Although no references were quoted, the firm which markets the product stated in its literature that clinical reports were obtained from twenty-three different observers: "Of seventy-three cases of allergic contact dermatitis which were not eczematous, sixty-two responded favorably. Six of eight cases of dermatitis due to poison ivy were relieved following local application of the cream. Of forty-five cases of allergic eczema, twenty-seven were reported as showing satisfactory response. Of seven cases of pruritus ani or pruritus vulvae, six had some degree of relief and one was not benefited. As a rule, urticaria and neurodermatitis were not improved to any significant degree. In some instances contact dermatitis responded better to both oral and local administrations of the drug than to local treatment alone. Sixteen cases of acute allergic dermatitis due to contact with various drugs cleared promptly upon application of the cream, but the dermatitis returned when contact with the allergenic drug was returned. One patient with eczema of the face of years' standing was relieved of itching within an hour, and the eruption had completely disappeared after three weeks' treatment. The allergen was thought to be egg, and contact with egg was being avoided. The eruption reappeared four months later and was again relieved by prompt resumption of treatment. One case of contact dermatitis was due to a rare chemical with which the patient was of necessity in contact at intervals of a few months. Relief was obtained by both oral and local administration. When contact with this chemical was again necessary, oral and local therapy was begun at the first appearance of dermatitis, with resultant relief." It is difficult for us to interpret these results.

Thephorin, the drug used in this investigation, differs chemically from the ethylenediamine derivatives (Antergan, Neo-antergan, and Pryibenzamine) and the closely related diphenylhydramine compounds (Benadryl and Hydryllin). Thephorin base is a brand of phenindamine which is a polycyclicamine. The oral forms of the drug, syrup and tablet, contain

the hydrogen tartrate salt of the Thephorin base which is also used in the ointment. The formula for the Thephorin base is 2-methyl-9 phenyltetrahydro-1-pyridindene.

In August 1948, Wooldridge and Joseph[11] reported the results of the use of Thephorin in the treatment of disseminated neurodermatitis. Their patients were treated with the syrup and tablets orally in addition to the topical use of 5 per cent Thephorin in a carbowax vehicle. Twenty-one patients were treated with both local and oral medications and two patients received only the ointment. The degree of involvement varied from that of a mild cubital or periorbital eruption to acutely pruritic and exudative eruptions involving most of the flexural areas. The duration of the disease varied from two weeks to seventeen years and the period of treatment from one to seven weeks. Treatment was carried out during the severest part of the winter and the results did not include any period during which spontaneous seasonal clearing, which is so often observed, could be noted among other such patients. The results of treatment were as follows:

Complete clearing	2
More than 75 per cent but less than complete clearing	7
More than 50 per cent but less than 75 per cent clearing	8
Benefited but less than 50 per cent clearing	2
Not benefited	3
Became worse (although patch tests were negative)	1

For a period of two weeks, three patients received Thephorin orally together with tars and other medications before Thephorin ointment arrived. No benefit attributable to oral Thephorin could be noted. A control series of six patients was also treated. One cleared completely with application of a carbowax base only, while the remaining five showed conclusive improvement in the areas treated with the Thephorin ointment but no improvement in those treated with the ointment base alone. In four of the twenty-three patients the oral medication was discontinued because of side effects of irritability and sleeplessness. In these patients the lack of oral medication did not seem to slow the rate of improvement. The authors believed that it was likely, in view of the consistent failure of previous antihistaminic drugs in the treatment of disseminated neurodermatitis, that Thephorin has a mode of action which is distinctly different from the others since it is not a significantly more powerful antihistaminic agent.

PERSONAL EXPERIENCE WITH THE TOPICAL APPLICATION OF THEPHORIN

The purpose of this study was to investigate changes in the subjective and objective signs in common dermatoses which could be obtained by the application of 5 per cent Thephorin incorporated in carbowax 1500.* Most of the patients were advised to apply the ointment thinly as frequently as was necessary to allay itching. Unmedicated carbowax 1500

*Supplied by Hoffmann-La Roche, Inc., Nutley, New Jersey.

was substituted for the Thephorin at times in an attempt to evaluate the psychologic effect of the therapy and the effect of the vehicle itself as a lubricant.

Sixty per cent of the fifty-eight cases which were treated with Thephorin ointment were circumscribed neurodermatitis. The average age was 39.3 years and there were 57 per cent males and 43 per cent females. The average duration of the disease was about five years. Most of the patients (38.2 per cent) had received previous therapy in the form of various topical applications including roentgen radiation as well as oral antihistaminics and sedatives. Approximately half of the patients presented single lesions while the rest had multiple plaques. Twenty-five per cent presented lesions on the anogenital region, 25 per cent on the neck, 25 per cent on the legs, 10 per cent on the nuchal region, 10 per cent on the arms, 5 per cent in the ears, and 5 per cent on the lids. Only one patient in thirty-four presented lesions on the trunk. The duration of treatment with 5 per cent Thephorin ointment varied from three days to three months. Forty-four per cent were treated one week or less; an additional 21.5 per cent from one to two weeks, and 34.5 per cent for periods varying from two to twelve weeks. The results following the application of Thephorin ointment were as follows:

	Objective	*Subjective*
Excellent	6 (17.6%)	6 (17.6%)
Moderate improvement	19 (55.9%)	22 (64.7%)
No change	5 (14.7%)	2 (5.9%)
Worse	4 (11.8%)	4 (11.8%)

Three patients reported relief of varying degree when the preparation was first used but within a short time the efficacy diminished so that some other preparation had to be used. One patient stated that the unmedicated carbowax 1500 base was equally effective as the Thephorin ointment and another believed that Pyribenzamine cream was equally effective as the Thephorin ointment. In one patient whose eruption flared following the use of the Thephorin ointment a patch test was negative at 48 hours. Two other patients developed folliculitis following the use of the preparation.

There were nine patients with disseminated neurodermatitis (atopic dermatitis). The average age was 24.5 years. Of this group 77 per cent were male and 23 per cent female. In 50 per cent of the cases the eruption had been present since infancy or childhood while in the others the duration of the eruption averaged over four years. All of the patients had been previously treated by various methods. Fifty-five per cent of the patients presented exudative lesions. The results were as follows:

	Objective	*Subjective*
Excellent	0	11.1%
Moderate improvement	55.5%	22.2%
No change	0	33.3%
Worse	44.5%	33.4%

One patient obtained symptomatic relief for one month, following which she flared and presented a positive patch test to the preparation.

The next group was made up of seven patients who presented eczematous eruptions which we were unable to classify. The results were as follows:

	Objective	*Subjective*
Excellent	43%	14%
Moderate Improvement	57%	86%
No change	0	0
Worse	0	0

The Thephorin ointment was also used topically in two cases of lichen planus, both of whom obtained definite relief from pruritus. In one the relief was striking. In one case of psoriasis involving the scalp, thighs, ankles, and perianal region there was relief from itching. One patient who had stasis dermatitis stated that a tar paste was equally effective as Thephorin ointment. One case of dermatophytosis of the feet and ankles was aggravated by the preparation and obtained no relief from itching. Another patient who had erythematosquamous seborrheic dermatitis of the ear canals obtained temporary objective and subjective improvement but flared six weeks after she had been using the ointment. A positive patch test was obtained. In a case of generalized idiopathic pruritus without cutaneous eruption there was no relief following the application of Thephorin ointment. Since the number of cases of each dermatosis in this miscellaneous group is so small it is impossible to draw conclusions regarding the value of Thephorin ointment.

In eighteen cases, 5 per cent Thephorin lotion was used rather than the ointment. The lotion was selected because the eruptions were acute, extensive, and exudative. Eleven of the patients were diagnosed contact dermatitis and seven, neurodermatitis. Five of the eleven patients had acute contact dermatitis due to poison ivy and all experienced prompt relief of pruritus. Two-thirds of the remaining six who had contact dermatitis experienced relief of itching. Three of the seven cases of neurodermatitis presented dry lichenified plaques while four showed more acute, eczematous lesions. Two of the three patients with dry lesions experienced relief of pruritus and to our surprise, all of the four patients with eczematized lesions were relieved. There were no exacerbations which were attributed to the application of the lotion.

COMMENT

Most of our cases were circumscribed neurodermatitis. We were especially interested in the antipruritic value of Thephorin ointment in this type of dermatitis. About 80 per cent of the patients obtained gratifying relief from pruritus. Many of these individuals stated that Thephorin ointment was far superior to any other topical application which they had used. Because of the fact that other agents, especially roentgen

radiation, were used we do not feel qualified to analyze the objective results. We believe that it is permissible to say that Thephorin ointment is an efficient antipruritic and only occasionally produces irritation. It is our distinct impression that the application is more effective in dry lesions and is more apt to aggravate exudative lesions. The ointment was especially effective in anogenital pruritus with lichenification (included in our group of circumscribed neurodermatitis). The objective and subjective improvement was excellent in thirteen out of the fourteen cases of this type.

Because of the relatively small number of cases of atopic dermatitis, far-reaching deductions cannot be drawn. We feel, however, that the preparation is relatively ineffective in this dermatosis since none of the cases obtained startling objective improvement and only 10 per cent excellent subjective improvement. There were a few other cases in which some improvement occurred but it is impossible to determine whether the improvement was the result of the application of the Thephorin ointment. In contrast, one-third of the patients complained that their symptoms were more intense and almost one half were objectively worse.

In the few cases of acute dermatitis in which Thephorin lotion was used it proved to be an effective antipruritic agent. We gained the impression that the lotion was more satisfactory than the ointment in exudative lesions.

From our studies we have been unable to elucidate the mode of action of Thephorin as used topically as an antipruritic. According to Bishop[1] itching is a modality of pain and is most easily elicited at central pain spots. He believes that itching represents a summation of weak subthreshold pain stimuli. Lehmann[7] has shown that Thephorin possesses a potent local anesthetic action. On the rabbit's cornea 1 per cent solution of Thephorin produced deep anesthesia lasting twenty-nine minutes. Using the intracutaneous wheal test on guinea pigs, Thephorin produced local anesthesia of longer duration than procaine hydrochloride. This may be the explanation of its antipruritic action in the human skin. The other possibility is that enough of the preparation penetrates the integument to produce an appreciable local antihistaminic effect.

CONCLUSIONS

1. On the basis of our experience, Thephorin used topically is an effective antipruritic agent in circumscribed neurodermatitis.
2. It is especially effective in anogenital pruritus with lichenification.
3. It is more effective on dry lesions and more likely to produce irritation on exudative lesions.
4. The topical use of Thephorin ointment in disseminated neurodermatitis (atopic dermatitis) was not particularly encouraging.
5. The number of cases of miscellaneous dermatoses was too small to draw any definite conclusions.

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POLLEN SURVEY OF LOS ANGELES 1941-1945

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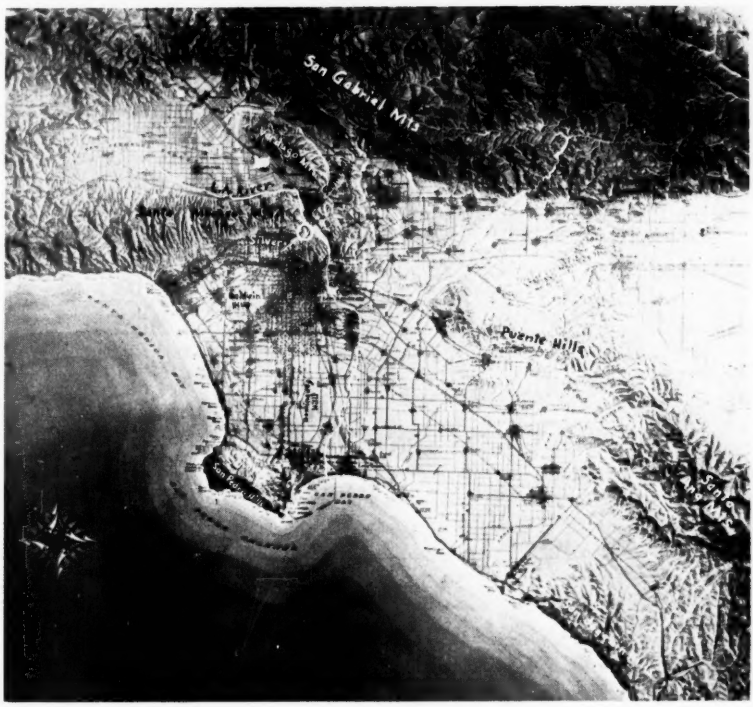
THE HAY-FEVER flora of the Los Angeles area has been adequately described[6,15,17] but information relative to the local pollen counts and seasons remains meager. Reports presently available[3,4,7,18] fail to encompass a year's period, or list total rather than differential counts, or exhibit both defects.



This paper presents the differential counts accumulated at a single station in Los Angeles over a period of five years.

METHOD

Since wartime exigencies made it impossible to use the roof of a tall building for the duration of this study, the place of exposure was a residence in the Silver Lake neighborhood. The exposure technique consisted

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TABLE I. TREE POLLEN COUNTS

		Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Yearly Totals	Highest Count And Date
Acacia	1941			3	4	2	3		1	1	1			15	
	1942		3	2	1	1	5	4						16	
	1943	1	2				2			2				7	
	1944		4	5	1		4		1					15	
	1945	4		1	1	1		1	1					9	
	Aver.													12	
Alnus (Alder)	1943	19	3											22	
	1944	26	1										2	29	
	1945	36	4											40	
	Aver.	27	3											30	
Cupressaceae (Cypress family)	1942	35	50	104	63	6							22	280	18, Apr. 3
	1943	10	52	49	36	3								150	8, Feb. 1
	1944	10	37	66	17	5							3	138	6, Mar. 11
	1945	9	44	15	16	4							12	100	8, Feb. 7
	Aver.	16	46	59	33	5							9	167	
Eucalyptus	1941		4	0	3	4	2	1	2	1		2	6	25	
	1942		1	3	1		1	1	1				1	9	
	1943	3	1	1	2	1				2			1	11	
	1944	1	1	1	1		1			2	1			8	
	1945	1	1	1	1	1		3	3			1		12	
	Aver.													13	
Juglans (Walnut)	1941			8	84	48	1							141	10, Apr. 8
	1942			39	91	67	3							200	18, Apr. 23
	1943			21	71	35	1							128	7, Apr. 1
	1944			39	143	52	4							238	19, Apr. 16
	1945		2	20	64	40	2							128	6, Apr. 28
	Aver.			25	91	48	2							167	
Olea (Olive)	1941				11	55								66	5, May 7
	1942				9	32	2							43	3, May 5
	1943				13	29								42	2, various times
	1944				7	37	1							45	4, May 3
	1945				8	33	3							44	2, various times
	Aver.				10	37	1							48	
Pinaceae (Pine family)	1941		4	52	15	5	2	1	2	5	1	1		88	8, Mar. 1
	1942	1	40	31	20	14	56	10	2	8	55	6	1	244	9, June 15
	1943		45	11	12	7	14	1	1	4	2			97	4, Feb. 14
	1944		21	59	13	8	16	7	5	4	69	14	1	217	5, Mar. 8
	1945	4	42	24	21	12	5	4	1	3	11	9	1	137	5, Feb. 17
	Aver.		30	35	16	9	19	5	2	5	28	5		157	
Platanus (Sycamore)	1942			10										10	
	1943			26	2									28	
	1944			14										14	
	1945		3	13	5									21	
	Aver.			16										18	
Quercus (Oak)	1941			50	81	48								179	16, Mar. 17
	1942		11	284	125	98								518	73, Mar. 27
	1943			30	49	7								86	9, Apr. 1
	1944		7	154	146	30								339	32, Mar. 30
	1945			10	86	10								106	6, Apr. 6
	Aver.			105	97	39								246	
Salix (Willow)	1943				6									6	
	1944				2	11								13	
	1945				2									2	
Ulmus (Elm)	1942								2	80	3	1		86	13, Sep. 10
	1943								4	10	6	3		23	2, Sep. 14
	1944									9	6			15	2, Sep. 25
	1945									3	37			40	15, Oct. 1
	Aver.								2	25	13	1		41	

TABLE II. GRASS POLLEN COUNTS

		Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Yearly Totals	Highest Count and Date
Gramineae	1941			22	80	130	81	95	55	53	71	29	10	626	11, May 26
	1942	2	5	28	44	142	158	205	92	93	78	18	5	870	12, July 7
	1943	1	2	20	59	147	81	105	88	68	62	19	10	662	16, May 14
	1944	1	3	23	67	119	59	24	77	28	30	7		438	7, few times
	1945	2	3	18	45	84	63	45	48	43	20	8	2	381	6, few times
	Aver.	1	3	22	59	124	88	95	72	57	52	16	5	595	

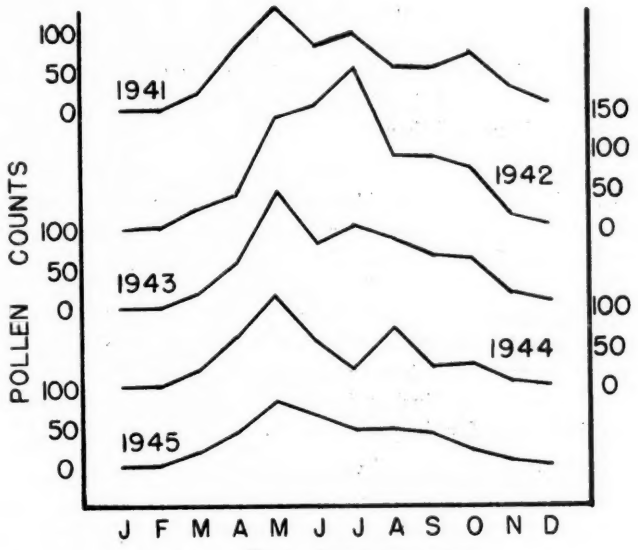

Fig. 1. Annual grass seasons.

in placing a vaseline-coated slide on a window sill of a roofed-over porch facing, and open to, the west. A slide was set out at approximately 8 a.m. every day when counts were relatively high, otherwise every two or three days. Pollen counting was done with the aid of an inclined binocular microscope with a 10X ocular and 10X (16 mm.) objective. The measured width of the field at this magnification was 1.6 mm. The standard slide being 1 x 3 inches, one sweep across the width of the slide covered an area of 40.6 (= 25.4 x 1.6) sq. mm., and five such sweeps an area of 203 (= 5 x 40.6) sq. mm., or approximately 2 sq. cm.

The counts presented in this paper are based on this area of two square centimeters.

While most of the pollen grains seen on the slides have been identified over the five-year period, a few are still of unknown origin. Some are seen unpredictably at rare intervals. Others, also minimal in number, are noted seasonally.

TREES

Table I presents the tree pollen counts. (In a few instances, e.g. alder, the counts for the first year or two were not carried out.)

The low numerical value of the counts in this and succeeding tables has necessitated a grouping of the data by months in order to obtain a meaningful picture of the seasonal fluctuations. This is in contrast to reports from other areas where the counts are grouped by periods of a few days.

In the case of *Acacia* and *Eucalyptus* the pollens appear in such few numbers sporadically throughout the year that no attempt has been made to determine their average monthly totals. (Pollen of the *Palmaceæ*, not listed in the table, similarly occurred in negligible quantity.)

An interesting finding with respect to elm is that the pollen was noted at this station only in the fall, not in the spring as in the East. The source of the pollen is discussed below.

GRASS

The counts for grass are assembled in Table II. Figure 1 depicts the seasonal fluctuations. The pattern of atmospheric incidence is as follows:

At rare intervals from mid-December through February, a single pollen may be noted as a wind-blown relic of the previous season. In March, the count begins to climb progressively upward until the height of the season is reached during the latter part of May and first part of June. From then onward to mid-December, the trend is downward, but temporary recrudescences may occur during this period. In fact, the July counts of 1942 were the highest for the year.

WEEDS

Table III summarizes the weed counts.

An unexpected finding is the definite, though minimal, increase in the ragweed count which takes place in the month of May in addition to the usual fall increase. This is clearly demonstrated in Figure 2.

Interesting also is the recurrence of artemisia pollen in January of 1942 and of 1944. Ordinarily, this pollen disappears from the air in early December. The phenomenon has been explained by the Smalls[17] as being due to the fact that in the foothills of the interior ranges the pollinating habit of *Artemisia californica* is different from that which the species exhibits on the coast. Inland, its pollination is dependent upon the rainfall, and when the fall precipitation is too light the plant awaits the heavier rains of late December or early January to complete its flowering.

Figure 3 shows the average seasonal fluctuations obtained at this station for the pollens of major clinical importance.

DISCUSSION

The observations reported above are similar to those reported from other areas of the South and Southwest with regard to (1) the occurrence of two annual atmospheric waves of ragweed pollen, (2) the presence of a

TABLE III. WEED POLLEN COUNTS

		Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Yearly Totals	Highest Count and Date
Ambrosieae (Ragweeds)	1941				3	8	1	8	5	33	40	3	1	118	5, Oct. 1
	1942				2	14	1		11	35	20	5	2	91	5, Sep. 21
	1943				2	13	2	5	11	46	18	2	1	100	4, Sep. 23
	1944				4	12	1	1	8	20	20	1	1	70	3, Oct. 4
	1945				6	5		1	3	29	23	3	0	74	6, Oct. 1
	Aver.				3	10	1	3	8	33	24	3	1	91	
Artemisia (Sagebrush)	1941							1	8	24	20	46		100	8, Nov. 8
	1942	3						1	1	9	8	19		38	3, Nov. 14
	1943							1	1	6	5	5	2	20	1, Various times
	1944	6						1	4	9	11	2	1	28	1, Various times
	1945								1	6	17	11	2	37	2, Oct. 24
	Aver.							1	3	11	12	17	1	45	
Chenopodiaceae-Amaranthaceae	1941			1	7	9	17	7	11	6	1			59	2, Various times
	1942			2	1	1	3	1	7	2	2			19	1, Various times
	1943			1	2	1		1	6	2				13	1, Various times
	1944			4	1	2	4	1	9	5	1			27	1, Various times
	1945				2	3	10	10	10	8	2			45	2, Various times
	Aver.			2	3	3	7	4	9	5	1			33	
Fern	1942							1	8	5	7	1	1	23	
	1943	1				1		2	5	10	6	6	2	33	
	1944								3	4	3	2		12	
	1945	1	2					2	6	3				14	

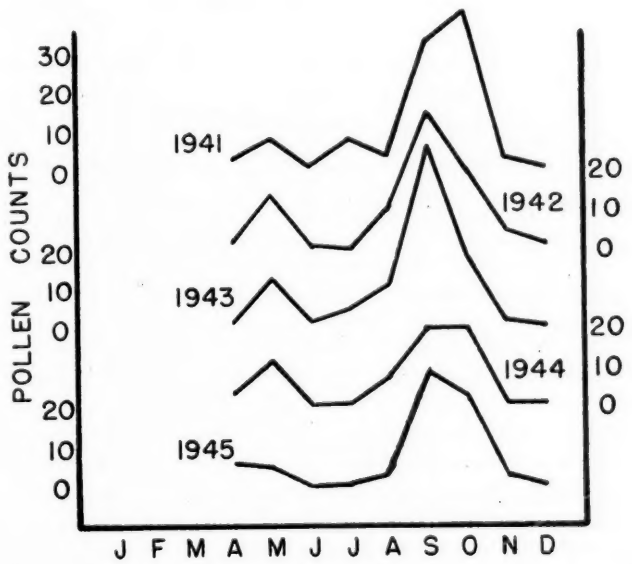

Fig. 2. Annual ragweed seasons.

fall-pollinating elm, (3) the prevalence of generally low counts and (4) the prolonged, overlapping seasons:

1. The phenomenon of two ragweed seasons for the year is engendered by the presence of various species of spring-flowering ragweeds coexisting

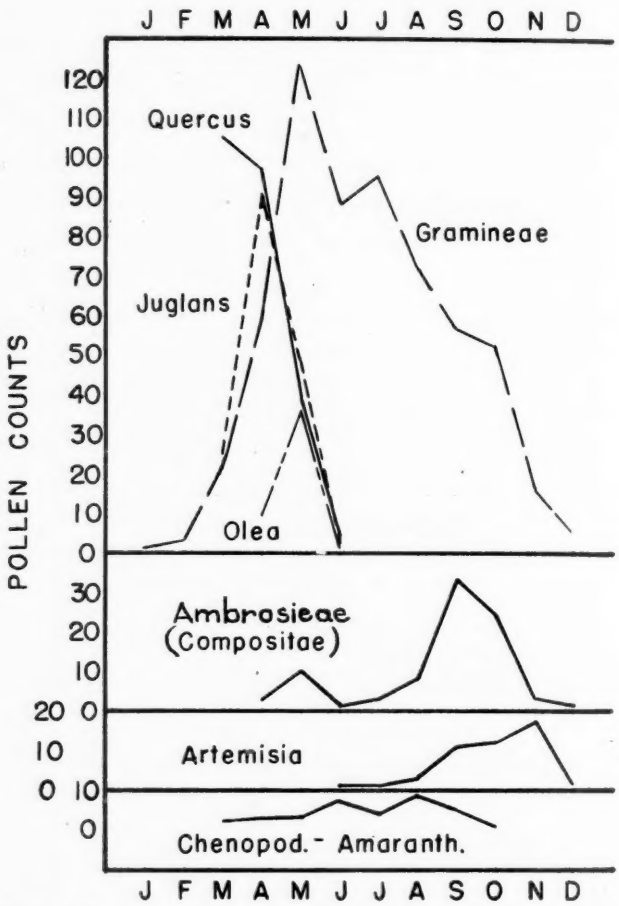

Fig. 3. Pollen seasons of Los Angeles, five-year averages, Silver Lake Station.

with the usual fall-blooming ones. Watson and Kibler[21] reported this spring ragweed season in the Southwest some years ago, and stated that it was due to *Franseria deltoides*. Phillips[13] later studied the matter more intensively and pointed out that additional spring pollinators such as *F. dumosa* and *F. ambrosioides* are present in the Salt River Valley, in which Phoenix is located, and that in other valleys farther south and west

Hymenoclea salsola similarly flowers in the spring. Durham,[5] on the basis of Rydberg's[16] study of the distribution of *F. dumosa,* states that a spring ragweed season is present in the Mojave Desert also, and southwestward from there to Lower California. This has been verified recently by Harsh,[9] who, in a zone made up of contiguous portions of California, Arizona, and Mexico, finds a spring ragweed season due primarily to *F. dumosa* and possibly also to *H. salsola.*

These desert ragweeds are not found in this coastal area. Here[6,15,27] the earliest spring-flowering composites of importance in allergy are *F. bipinnatifida* (beach bur), *Xanthium canadense* (cocklebur), and *Xanthium spinosum* (spiny cocklebur).

The two species of *Xanthium* may be dismissed from consideration as contributing to the spring rise in atmospheric ragweed pollen. For one thing, the distinctive pale "pebbled" grains of cocklebur have up to this time not been noted at this station. But more decisive than the restricted distribution of the genus is the fact that field observations reveal that the peak of pollen production of both species is not reached till midsummer* or after.

F. bipinnatifida, on the other hand, ranges all along the coast of California, and while it blooms at any time from April into fall, it may be observed that optimum opportunity for collection of its pollen generally takes place in early May.* The conclusion is inescapable at the present time that this species must account almost entirely for the spring wave of ragweed pollination.

The situation here thus duplicates what has been reported from San Diego County by Harsh.[8] At Alpine, California, Harsh finds that a striking rise in ambrosia-like pollen occurs during April and May, and he concludes that this can come only from *F. bipinnatifida.* The charts in his report show that a spring ragweed season takes place in the city of San Diego too, and Stealy's[19] charts of the atmospheric pollen of San Diego for 1936 likewise reveal this phenomenon.

While the two ragweed seasons in the desert are separated by a time interval, during which no pollination occurs, climatic conditions here induce *F. bipinnatifida* to flower continuously or remittently into the fall so that its flowering season ultimately merges with that of the late summer and early fall-blooming species (*Franseria acanthicarpa, Ambrosia psilostachya*). Except for July of 1942 and June of 1945, ragweed pollen was found on the slides each month from April through November of each year, albeit in minimal or negligible quantity during the summer months. The exaggerated spring outburst of pollination must be attributed to a characteristic pollinating habit of *F. bipinnatifida* in this latitude. Obviously, vagaries in this pattern of pollination may be expected to take place contingent upon weather conditions. Thus, in Figure 1, one sees an

*Personal communication from Mr. M. E. Webb, Hollister-Stier Laboratories.

additional wave in July of 1941, and in April of 1945 the count was as high as for May.

The occurrence of a definite rise and fall in the amount of atmospheric ragweed pollen in the spring has not previously been reported from Los Angeles. The finding demonstrates once again the necessity of making routine pollen counts in addition to field observations in order to establish local patterns of fluctuation in air-borne pollen incidence. Such patterns cannot be deduced from field observations alone.

2. The presence of a fall pollinating elm in the Los Angeles area has likewise not been previously commented upon in the literature of allergy. Black and Durham[1] have reported the presence of two fall-pollinating species elsewhere in the South, *U. crassifolia* (in the central and northern portion of Texas, and adjoining portions of Oklahoma and Arkansas) and *U. serotina* (in Tennessee and adjoining states).

The species here is *Ulmus parvifolia.* This species has the striking characteristic of not being deciduous in this climate, although in very cold weather it may tend to drop some leaves. For this reason, it is sometimes termed the evergreen elm, or evergreen Chinese elm to differentiate it from *U. pumila* (Siberian or dwarf Asiatic elm) which in lay parlance is also sometimes called Chinese (or dwarf Chinese) elm. Horticulturists here distinguish also a variety of *U. parvifolia* which is called *U. sempervirens,* a tree which is purported to have a more droopy habit and smaller leaves than *U. parvifolia.* The fact that it is not deciduous has made the evergreen elm by far the most popular and predominant one here in recent years, so that it greatly outnumbers other species encountered to date. These, in order of frequency, are *U. pumila, U. americana,* and *U. campestris* (English elm). The last named is quite rare. The American elm is noted only occasionally except in Beverly Hills. This municipality occupies an area of about five square miles within the confines of Los Angeles, its central portion being located approximately eight miles from this station. Within this territory, the Beverly Hills Park Department has planted almost 4,000 specimens of *U. americana.* Despite this massed stand, it is of interest that no elm pollen has been noted on the slides in the spring.

Predominance of *U. parvifolia* is not confined to Los Angeles, but is reported from other Southern California communities as well.*

In view of the reputed[1] allergenic potency of its pollen, it is apparent that the elm must be kept in mind as a potential factor in clinical allergy in both spring and fall in this area.

3. The lack, up to the present time, of standardized techniques of exposure and counting makes it difficult to compare with any exactness the

*In Pasadena,[2] only one other species is stated to be present: *U. pumila.* In Santa Barbara,[30] two others are listed: *U. americana* and *U. campestris.* In Santa Monica,[10] Hastings describes five others: *U. americana, U. campestris, U. foliaceae, U. hollandica,* and *U. pumila,* so that this community contains six of the nine species which McMinn and Maino[31] state are present on the Pacific Coast, the three others being *U. alata, U. fulva,* and *U. glabra.*

counts obtained here with those reported from other parts of the country. It is obvious however that for most part the counts here are minimal. To midwest allergists this is particularly noticeable in the case of ragweed. Such low counts tend to be misleading with respect to the incidence of clinical allergy here, so that it is not amiss to emphasize again, as was done previously by Piness[14] and by Stealy,[19] that there is no dearth of clinical pollinosis in Southern California. It is evident that our minimal counts are adequate to induce sensitization, although they may ensure that the severity of the resulting symptoms is less, generally speaking, than is the case in high count areas.

4. The tables reveal that as early as April one may encounter in the air such diverse pollens as those of the amaranth-chenopod group, the grasses, and ragweed in addition to the usual tree pollens such as oak, walnut, and olive. As late as October, one may still find represented the amaranth-chenopod group and the grasses, in addition to the usual fall types, such as artemisia and ragweed. These prolonged seasons are of course a function of the climate and have been reported from other favorable climates, as for example those of New Orleans[12] and Florida.[22] Wodehouse,[22] in this connection, has vividly portrayed the effect of southern latitudes in altering permanently the pollinating habit of ragweed from that shown by the plant in the north.

The data of this survey may be considered as being reasonably accurate for the Los Angeles coastal plain, but a problem that invites consideration is that of the possible variations to be met with in the surrounding territory. The topography of Southern California is featured by a remarkable diversity over relatively short distances. The resulting differences in conditions of temperature, humidity, precipitation, and altitude may produce a noticeable alteration, as the Smalls[17] have pointed out, in the flowering times of certain species within the short span of miles between the coast and both the foothills and heights of the interior mountain ranges. The degree, therefore, to which the present findings reflect the situation in areas adjacent to the coastal plain can be determined only by carrying out the manifest need for pollen surveys from several different stations.

As for the possible clinical importance of the unidentified pollens observed on the slides, one may state without hesitation that their role, if any, in the production of allergy must be minor. This is so not only because of their infrequent appearance and few numbers, but, what is more important, no distinct group of cases has as yet been delineated which parallels the time of appearance of these unknowns.

SUMMARY

A five-year study of the atmospheric pollen concentrations and pollen seasons at a single station in Los Angeles reveals that the pollen counts are low, and the seasons more prolonged and overlapping than in the Midwest and East.

The pollens of the trees are dispersed throughout the year as follows: Acacia and Eucalyptus, on intermittent occasions at any time of the year. Cypress family, beginning somewhat before the first of the calendar year and continuing through April. Alder, chiefly during January. Pine family, February through November. Sycamore, March and part of April. Oak and walnut, from approximately the first of March through May. Willow, on occasion during April. Olive, middle of April to the first part of June. Elm, latter part of August into October.

Pollen of grass is noted very rarely in the period from mid-December to March. The count then increases rapidly to a peak during the latter part of May and first part of June, then declines gradually, with some recrudescences, over the remaining months to mid-December.

Pollen of the chenopod-amaranth group is found from March through October with somewhat increased incidence from June through September. Ragweed pollen occurs from April through November and gives rise to two seasonal waves: a minimal one in May, generally, and a maximal one from the latter part of August through October.

Sagebrush pollen is present from July into December, with a definite seasonal upswing during September, October, and November. In some years, a brief recurrence in January takes place.

I am indebted to the following for help in preparing this paper: Prof. O. A. Plunkett, Department of Botany, University of California, Los Angeles; Prof. W. C. Putnam, Department of Geology; Mr. J. Dorfman; Mr. Samuel Miller, Senior Observer of the U.S. Weather Bureau, Los Angeles; and Mr. M. E. Webb of the Hollister-Stier Laboratories.

REFERENCES

1. Black, J. H., and Durham, O. C.: Elm pollen as a complicating factor in hay fever. J. Allergy, 1:501, 1930.
2. City of Pasadena Park Department: Official Street Tree List, 1940.
3. Deamer, W. C., and McMinn, H. E.: Studies in atmospheric pollen of San Francisco. J. Allergy, 6:480, 1935.
4. Durham, O. C.: The pollen content of the air in North America. J. Allergy, 6:128, 1935. (See also Table 10, p. 172, in Feinberg, S. M.: Allergy in Practice. Chicago: The Year Book Publishers, Inc., 1944).
5. Durham, O. C.: p. 183 in Feinberg.[4]
6. Hall, H. M.: Hay-fever plants of California. U.S. Public Health Rep., 37:803, 1922.
7. Hara, H. J.: Hay fever among Japanese: II. Arch. Otolaryng., 21:9, 1935.
8. Harsh, G. F.: Pollinosis in San Diego County, California. Ann. Allergy, 3:27, 1945.
9. Harsh, G. F.: Pollinosis in Imperial County, California, and Yuma, Arizona. California & West. Med., 64:245, 1946.
10. Hastings, G. T.: Trees of Santa Monica. Published by the author, Santa Monica, California, 1944.
11. McMinn, H. E., and Maino, E.: An Illustrated Manual of Pacific Coast Trees. Berkeley, Calif.: Univ. of Calif. Press, 1937.
12. Penfound, W. T., Efron, B. G., and Morrison, J. J.: A survey of herbaceous plants in New Orleans in relation to allergy. J. Allergy, 1:369, 1930.
13. Phillips, E. W.: Pollen incidence in central Arizona. J. Allergy, 3:489, 1932.
14. Piness, G.: Study of two hundred and two cases of hay fever. J.A.M.A., 84:584, 1925.

(Continued on Page 722)

THE HEART IN BRONCHIAL ASTHMA

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THE difficulty in diagnosing bronchial asthma, especially in advanced age, lies in differentiating cardiac and pulmonary asthmatic involvement. We have various laboratory and diagnostic tests—blood eosinophilia, intradermal, patch-tests—which are supported by experienced history-taking to avoid serious mistakes that may influence the success or failure of the proposed treatment of the case in hand. Nevertheless, there are certain border states where cardiac and asthmatic conditions appear side by side. The purpose of this report is to point out how far cardiac and circulatory changes follow the asthmatic state without actual primary myocardial damage.

The first question in considering the heart and circulation in bronchial asthma is whether the physical and electrocardiographic changes are due to anaphylaxis and allergy, or whether they follow secondary pulmonary congestion, failure of the right ventricle, anoxia, occasionally emphysema and structural abnormalities, such as asthenia, drop-heart, and scoliosis.

Several authors mention cardiac relationship between bronchial asthma and its closely related clinical conditions. The origin of typical electrocardiographic changes was studied by Kallós. In experimental asthma of rabbits, he came to the conclusion that such changes followed myocardial anoxia and reflex coronary spasm leading to functional disorders. Such abnormalities persisted only as long as the asthmatic attack lasted, and structural changes were infrequent. Mainzer, Krause, Harkavy, Romanoff, Urbach, Loew and Gottlieb studied similar conditions in human beings. They found that while myocardial anoxia was present only as long as the attack lasted, varying degrees of defective conduction and functional lesions persisted for days, weeks, and even permanently. This condition is considered to be allergic coronary disease or anoxic myocardial lesion. It may be explained by secondary conditions complicating asthmatic state—infection, increased cardiac strain and excess of drugs. Experiments confirmed this theory, inasmuch as administration of caffeine during artificially established asthmatic attacks induced myocardial lesions (Knepper, Page 1).

Zárday stated that electrocardiographic changes are due to relative ischemia, meaning that the amount of blood supplying the heart at rest becomes inadequate in excessive strain and stress (relative coronary insufficiency). Such overwork may be established by tachycardia in hyperthyroidism and by administration of epinephrine, i.e., sympathomimetic hormones increasing the O_2 demand of heart-muscle cells. Coronary ischemia may follow allergic inflammatory conditions (focal dis-

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TABLE I. AGE OF PATIENT AT FIRST ASTHMATIC ATTACK

Age	Number of cases
0-15 years	24
16-30 years	92
31-45 years	122
46-60 years	50
61-75 years	13

ease). Excessive administration of epinephrine leads to coronary insufficiency, increasing the blood flow and impeding thrombus formation, and so explaining relative rarity of coronary thrombosis and infarction of asthmatic patients. In our series of 301 cases, we found this condition only once. Excess of epinephrine may produce hemorrhage of the intima leading to coronary apoplexy (Master). Tachycardia in asthma derives from increased excretion and administration of epinephrine. One cause of sudden death in asthmatic individuals is overdosage of epinephrine or morphine; another cause according to Facquet-Claisse, being suffocation. Thus the fatal condition which leads to sudden death in asthma is probably ventricular fibrillation.

K. Hajós emphasized the importance of the asthmatic constitution, as well as the simultaneous occurrence of emphysema and drop-heart associated with the asthenic habitus. Several authors mention drop-heart as an important structural factor, and report special emphysematous electrocardiographic features. Master thought the drop-heart to be due to depression of the diaphragm in emphysema.

Winternitz and Olaf explained increased auricular activity with right axis deviation by right auricular preponderance. Wide, peaked P waves in the second and third leads associated with flattened P waves in the first lead point towards deviation to the right of the P wave axis.

Cooke found elongation of the QS conduction time, splitting of the QS segment and tachycardia to be the characteristic features of the electrocardiographic pattern in bronchial asthma.

In the following review of 301 mainly allergic asthmatic patients I wish to discuss the relationship between electrocardiographic findings and the cardiac state.

In dealing with the heart and circulation we considered the following criteria:

History: (1) age at first asthmatic attack; (2) duration of the asthmatic state at the time of our investigation.

Physical examination: heart size, heart sounds, murmurs, pulse rate, blood pressure, condition of lungs, structural deformities.

X-ray of heart and lungs.

Electrocardiographic findings.

Table I shows that 71.3 per cent of 301 patients developed their first

TABLE II. DURATION OF ASTHMATIC STATE AT TIME OF INVESTIGATION

Years	Number of cases
0-10	192
11-20	71
21-30	28
31-40	8
over 40	2

asthmatic attack between the years of fifteen to forty-five; diagnosis of asthma is more difficult in patients over forty-five years of age because of pulmonary and cardiac involvement. Faragó found that, although there had been no asthmatic symptoms in earlier years, the presence of certain structural deformities, such as drop-heart, had been habitual findings indicating an asthmatic constitution.

Table II shows that in 64 per cent of our cases the asthmatic state had been established approximately four to five years; in twenty-three (6 per cent) from ten to twenty-six years.

The physical examination was normal in 36.6 per cent. Important auscultatory findings were low, dull heart sounds independent of presence or absence of emphysema. Murmurs were less frequently noticed; i. e., an apical systolic murmur had been audible in 8.3 per cent, an aortic systolic murmur in 1 per cent, while an apical diastolic murmur could be heard in only one case. Accentuation of the pulmonary second sound occurred in 4.6 per cent; accentuation of the aortic second sound in 2 per cent.

Changes of pulse rate are significant for bronchial asthma. Tachycardia was noted in 34.6 per cent of our cases (over 100/min.), and only 2 per cent had bradycardia (below 60/min.).

Blood pressure readings showed similar changes. In 48 per cent, we found low systolic pressure (80 to 120), while hypertension had been established in 14.3 per cent (generally in advanced age and with doubtful asthmatic cases). Blood pressure had been physiological in 38 per cent.

Characteristic changes of pulse rate and blood pressure follow the asthmatic state and its treatment (epinephrine-effect). Furthermore, such changes may be stimulated by the asthmatic-asthenic constitution itself. It is well known that allergic reactions are associated with a fall in blood pressure. These symptoms are the result of allergic factors, endocrine function and constitutional disposition, or of the effect of drugs (theophylline, xanthine derivatives, barbituric acids).

In examining the lungs, we found various degrees of emphysema in 61.6 per cent, with associated percussory and auscultatory signs.

Emphysema associated with the asthmatic state may be primary, or it may be a secondary manifestation due to forced expiration. Naturally, emphysema complicates the asthmatic state under all circumstances because

of its influence on the heart and circulation. Acute or chronic cor pulmonale may follow severe cases. Signs of even slight emphysema at the beginning or after short duration of asthma may be detected on the electrocardiogram tracing pointing towards aggravation of symptoms.

In evaluating electrocardiogram tracings we should not forget that however exact this method of investigation may seem, it does not suggest in itself cardiac abnormality. Simultaneous fluoroscopy determines how far these changes follow structural abnormalities or whether they are merely secondary cardiac involvements of the severe asthmatic state.

Correct interpretation of electrocardiogram findings can be realized by the aid of simultaneous x-ray studies. Right axis deviation, inverted T waves, low voltage, changes in the ST segment could easily be taken for myocardial damage, although their only cause may lie in the shape and size of the heart, development of the thoracic cage, and emphysema.

X-ray studies of asthmatic patients confirm frequency of drop-heart with emphysema. We found this combination in 14.3 per cent of our cases without any auricular or ventricular enlargement. Left heart preponderance occurred in 9 per cent and enlargement to the right in only one case. Left ventricular preponderance had been present in 3 per cent, mitral and aortic configuration respectively, on one occasion; horizontally placed heart in 2.6 per cent. Drop-heart generally followed asthenic habitus; aortic configuration was associated with elongation and widening of the aorta. Auscultatory changes of the left side of the heart, particularly left ventricular preponderance, were apical systolic murmurs and accentuation of the pulmonary second sound.

The asthmatic habitus is generally congenital. In advanced age it is difficult to discern whether asthmatic constitution had been established previously to sensitizing factors.

Exact data concerning cardiac conditions could be acquired by autopsy. The difficulty lies in the fact that relatively few die from an acute asthmatic attack, and at autopsy we encountered only secondary asthmatic involvements. In our few autopsied asthmatic cases, we were unable to detect any changes characteristic of the asthmatic state (Radó). We finally came to the conclusion that either a central nervous effect or excess of drugs was responsible for sudden death in asthma, and not allergic reactions of the coronary system, as thought earlier.

Although electrocardiographic investigation gives the most exact solution of definite cardiac and circulatory changes in asthma, it is difficult to determine slight changes. We have to take the patient as a whole and consider the state of heart and circulation during the progress of the disease. We should consider secondary cardiac states responsible for transitory electrocardiographic changes and slight symptoms of no special importance.

Right axis deviation, as mentioned by the great majority of authors, is

one of the principal changes seen in electrocardiographic tracings. Kahn thought it to be due to right ventricular enlargement; Boas and Mann noticed right axis deviation in chronic cor pulmonale; Alexander Luten and Kountz found it without actual cardiac enlargement. Master stated that even in hypertensic patients over fifty years of age, right ventricular enlargement was preponderant.

In our own cases, the following electrocardiographic changes were the most conspicuous:

1. Right axis deviation.
2. Peaked, wide P waves in the second and third lead (P pulmonale, increased right auricular activity).
3. Depression of the ST segment and inverted T waves in the second and third lead.
4. Splitting of R and S waves.

Elongation of the QS conduction time was noteworthy, but was less frequently encountered.

Right axis deviation was well defined in 44.3 per cent of our cases, while left axis deviation was present in only 28.3 per cent; there was no axis deviation in 27.6 per cent.

We came to the conclusion that asthma, in itself, does not change the cardiac configuration, but secondary involvements, such as pulmonary congestion, structural deformities, and associated cardiac disease, are responsible for the enlargement of the conus and pulmonary artery (which Parkinson and Hoyle demonstrated in oblique x-ray views), as well as for right cardiac hypertrophy and right axis deviation. Aortic and mitral configuration are a sequel to valvular disease independent of asthma.

Cardiac enlargement, especially to the left, depended upon the grade of pulmonary involvement. Right cardiac strain in asthma and emphysema established overwork of the whole heart (acute cor pulmonale), and was responsible for changes of the ST segment and T wave.

Among changes in the ST segment, depression is the most frequent, having occurred thirty-eight times in the second, and thirty-one times in the third lead.

Convexity of the ST segment was prominent in forty-one cases in the second, and thirty-three times in the third lead. Depression of the ST segment occurred twenty-three times in the first lead, and convexity fourteen times in the same lead. Depression of the ST segment in the second and third lead was generally associated with inverted or diphasic T waves of the same leads. It seems to be noteworthy that T waves were flattened ninety-three times in the first, and only seventy-four times each in the second and third leads. We found inverted or diphasic T waves in forty-four cases in the third lead, and four times in both the second and third

lead. We must bear in mind that in bronchial asthma flat T waves in the first lead more frequently indicate myocardial damage than the inverted T waves of the third and even second lead.

Although we had to diagnose myocardial lesion in some cases, we should not forget that inverted T waves and depression of the ST segment in the third or even in the second lead are a sequel to high-graded right-axis deviation. Signs indicating coronary insufficiency generally follow local ischemia and do not mean actual coronary lesion, inasmuch as symptoms of the latter condition are usually permanently present, while changes due to the asthmatic state are reversible and disappear with the acute asthmatic attack. We proved the reversibility of asthmatic coronary spasm in our experiments, where five to six minutes after subcutaneous injection of 0.0005 gm. of epinephrine the heretofore inverted T waves became upright.

The QRS segment displayed changes of pattern in our electrocardiographic tracings. We found that partial interventricular block with elongation of the QS conduction time (over 0.09 to 0.10 seconds) in seventeen cases, was generally followed by splitting of the R and S waves in the second and third lead (splitting of the R wave seven times in the third, four times in the second, and once in the first lead). These changes are probably based on secondary right ventricular hypertrophy, which establishes delayed conduction in the interventricular septum. Although complete heart block is rare, we found partial bundle branch block in several instances, right bundle branch block once, left bundle branch block three times, and one case each of Wilson and arborization blocks.

In advanced state of emphysema, T waves become inverted in the second and third lead (right ventricular dilatation and hypertrophy), and right auricular preponderance ensued with large P waves in the same leads. We found peaked, high P waves in 23.3 per cent, even in otherwise low voltage electrocardiographic tracings.

All these changes finally lead to right ventricle failure with pulmonary hypertension. Left axis deviation is always of cardiac origin, such as coronary disease with hypertension and left ventricular enlargement. In one of our cases we found right axis deviation during the first decade of the asthmatic state; when secondary left heart failure had been established, the electrical axis deviated to the left.

We found elongation of the PR conduction time (over 0.20 seconds) based on right auricular preponderance in twelve cases.

Low voltage, as another change of the electrocardiographic pattern, was noticed in 7.3 per cent. As right axis deviation had been generally associated with high voltage, its percentage may be compared with the above-mentioned number.

As to heart rhythm, 94 per cent had normal sinus rhythm, of which 63.6 per cent were of normal frequency; 34.4 per cent had sinus tachycardia, and 2 per cent sinus bradycardia. Abnormalities of rhythm were

present in 6 per cent; seven cases of ventricular, four supraventricular, one auricular and one mixed form of ectopic beats. We found four cases of respiratory arrhythmia, and one with nodal rhythm.

Tachycardia follows the asthmatic state, vasomotor lability, and excess of epinephrine. Tachycardia and pulse pressure may rise to such a degree as to simulate hyperthyroidism. Frequently we encountered increased basal metabolic rate with increased thyroid function.

By means of the electrocardiogram the possibility of myocardial damage was generally excluded and myocardial lesions were found in only 25.3 per cent.

SUMMARY

1. Discussion of 301 cases of bronchial asthma with respect to cardiac and circulatory changes associated with structural, pulmonary, and specific asthmatic conditions.

2. Characteristic electrocardiographic tracings in asthma were found to be due to secondary manifestations, and not to special allergic reactions.

3. Abnormalities of heart and circulation meant less frequent actual damage in asthma than in other conditions.

4. The heart may be involved in bronchial asthma to a lesser extent than in associated valvular lesions, although the asthmatic state may aggravate established heart failure.

5. It must be emphasized that, especially in bronchial asthma, the electrocardiogram *per se* cannot give a true picture of the heart, and therefore the entire individual must be taken into consideration.

Acknowledgement and thanks are extended to Drs. Bien, Gara, László and Radó for their help in taking the electrocardiographic tracings recorded above.

REFERENCES

Best, Ch. H., and Taylor, N. B.: The Physiological Basis of Medical Practice. Baltimore: William & Wilkins Co., 1945.
Cooke, R. A.: Allergy. Philadelphia: W. B. Saunders, 1947.
Faragó, P.: Das Asthma des vorgeschritten Alters. Deutsche med. Wchnschr., No. 12, 1938.
Hajós, K.: Die Rolle der konstitutionellen und konditionellen Faktoren in der Pathogenese des Asthma bronchiale. Wien. Arch. f. Inn. Med., 13 B, 1926.
Hajós, K., and Rajka, Ö.: Asthma, Ekzema, et cetera. Budapest: Eggenberger, 1944. (In Hungarian).
Hansen, K.: Allergie. Leipzig: Georg Thieme, 1943.
Haynal, I.: Diseases of Heart and Circulation. Budapest: MOKT. 1938. (In Hungarian).
Kallós, P., and Ewert, B.: Cardiologia, 2:147, 1938.
Kallós, P., and Kallós-Deffner, L.: Modellversuche zum Verständnis des allergischen Bronchialasthmas. Acta med. Scandinav., 116:5 and 6, 1944.
Master, A. M.: Electrocardiogram and X-ray. 2nd ed. London: H. Kimpton, 1946.
Sigler, L. H.: The Electrocardiogram. New York: Grune & Stratton, 1946.
White, P. D.: Heart Disease. 3rd ed. New York: Macmillan, 1947.
Zárday, I.: The Electrocardiogram. Budapest: Eggenberger, 1944. (In Hungarian).

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NETHAPHYL IN BRONCHIAL ASTHMA

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THE reason for presenting this subject is aptly summarized by Loveless,[3] who said, "The need is so great for agents which will relieve asthma without the involvement of the hypodermic syringe or complicated inhalation apparatus that any addition to our armamentarium should be welcomed."

In comparison to Hansel's[2] 750 patients, the present series of forty indeed looks small. However, the purpose of this series was not to test the efficacy of Nethaphyl (Merrell) in bronchial asthma *per se* but rather to test its usefulness in asthmatic patients who had been perfectly well satisfied with the temporary relief they obtained with various ephedrine preparations—particularly Tedral and less often Amodrine or capsules of Ephedrine and Amytal.

The Nethaphyl tablets are scored and each contains Nethamine (methylethylaminophenylpropanol) hydrochloride, ¾ gr., and Butaphyllamine (theophylline aminoisobutanol), 2 gr. Nethaphyl with phenobabital tablets contain, as well, phenobarbital, ¼ gr. to each. The Amodrine tablets (Searle) each contain Racephedrine hydrochloride, ⅜ gr., Aminophyllin, 1½ gr. and phenobarbital, ⅛ gr. The Tedral Tablets (Maltine) each contain ephedrine hydrochloride, ⅜ gr., theophylline, 2 gr. and phenobarbital, ⅛ gr. Ephedrine and Amytal capsules (Lilly) each contain ⅜ gr. ephedrine and ¾ gr. amytal. The action of theophylline and aminophylline is well known. Butaphyllamine contains approximately 67 per cent theophylline, is possibly more stable and soluble than similar compounds and in toxicity on the experimental animal compares favorable with aminophylline.[5] Both Racephedrine and Nethamine hydrochloride have essentially the pharmacological action of ephedrine except for producing no noticeable pressor action and minimal central stimulation.[1,4]

Our observations were made on forty middle-aged, male asthmatic patients selected at random from those classified as infectiously asthmatic and receiving vaccine therapy. The specific therapy used in these cases will be described later in another paper. All of these patients had been taking Tedral tablets regularly or irregularly for as long as 11 years when they were first referred to us. The first change in regimen was the use of the tablet only when needed (i.e., for definite asthma). Later substitutions were: (1) a capsule containing ephedrine and Amytal, (2) Amodrine tablets, (3) Nethaphyl and (4) Nethaphyl with phenobarbital.

From the Allergy Clinic of Brown General Hospital, Veterans Administration, Dayton, Ohio, and published with the permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

All patients preferred Nethaphyl with phenobarbital over the plain Nethaphyl, due to the added sedative action. Of the forty, one preferred Amodrine to the others, one preferred the capsules containing ephedrine and Amytal, three preferred Tedral tablets and thirty-five preferred or were content with the relief obtained with Nethaphyl with phenobarbital. It is stated "preferred or were content" as these patients were asked if they again wanted ephedrine or were satisfied with the speed and completeness of the relief obtained with Nethaphyl with phenobarbital.

Very few of these patients had seen an allergist prior to being referred to us, and the use of Tedral for asthma has become common among general practitioners. It is not our purpose to condemn any of the ephedrine-containing mixtures. These preparations are useful, effective and dependable, but they have certain disadvantages. First, after some time, frequently the dose must be increased to obtain the same effect—later, a point is reached where satisfactory relief is not obtained regardless of dose. Second, in men of upper middle and old age, ephedrine often, on frequent use, causes a spasm of sphincters, producing a urinary retention. Third, ephedrine increases the blood pressure and pulse rate. Fourth, there is often produced increased nervousness over that already present in asthma, exhibited by a definite tremor of the outstretched fingers.

Discussing this point by point, Nethaphyl also must be increased after being used for some time, but we have found that when ephedrine loses its effectiveness, Nethaphyl gives relief, and *vice versa*, so that with manipulation constant alleviation of asthma may be obtained. No cases of urinary retention occurred while our patients were taking Nethaphyl and those caused by ephedrine definitely diminished. In none of our patients was blood pressure elevated or did tachycardia occur following Nethaphyl. All remarked about the lack of tremor and nervousness and some wondered how they obtained relief without these symptoms. Also there were no toxic manifestations so it was unnecessary to stop the drug in any case for this reason.

Adversely, it must be stated that the action of ephedrine is slightly faster and the relief a bit more complete than with Nethaphyl. Chewing the tablets has hastened the action. Patients, though, prefer Nethaphyl and the somewhat reduced relief, to ephedrine and the side reactions.

Amodrine in our hands did not give adequate relief in most patients though it also did not cause palpitation, tachycardia, rise in blood pressure or nervousness.

SUMMARY

1. In a series of forty intrinsically asthmatic patients, thirty-five preferred Nethaphyl with phenobarbital to Amodrine, Tedral or Ephedrine with Amytal.

(Continued on Page 683)

A CLINICAL EVALUATION OF ORTHOXINE IN THE TREATMENT OF ALLERGIC DISEASES

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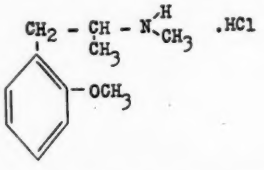
ORTHOXINE is a registered trademark of The Upjohn Company for a new synthetic amine (B-orthomethoxyphenylisopropyl methylamine hydrochloride).

The sympathomimetic amines have found a wide field of usefulness in medicine, particularly in the control of allergic diseases. After the chemical structure of epinephrine was determined, extensive studies on compounds related to it were made.[1,2,5,6] The pioneer investigations of Barger and Dale[3] led to the discovery of many useful compounds and stimulated the great interest in synthetic drugs.

Heretofore the selection of these compounds was based upon the degree of vasopressor activity. Following the discovery of ephedrine, further studies have developed many new and useful therapeutic agents. It is evident that a bronchodilator substance, free from pressor and central nervous stimulation effects, would be valuable for clinical investigation in asthma.[4]

Orthoxine was selected from a considerable number of synthetic amines because when compared to ephedrine sulfate in a large series of animal experiments, Orthoxine has (1) an oral activity comparable to ephedrine, (2) carries no central nervous system excitatory effects, (3) has no pressor action; in fact, appears to be slightly depressor, and (4) exhibits no cardiac effects of altering pulse, either slowing or accelerating.

Orthoxine has the following structural formula:



This is a pure white crystalline substance with a molecular weight of 215.5 and a melting point of 126.5° C. It is soluble in water, alcohol, ether and slightly soluble in ethyl acetate. It is insoluble in petroleum ether, benzene and toluene.

For oral use the salt* was furnished both as a compressed scored tablet,† 100 mg. (1½ grains) and syrup Orthoxine (each fluid ounce contains 300 mg. or 37.5 mg. (3/5 grains) to the teaspoonful.

*Supplied through the courtesy of The Upjohn Company.
†Orthoxine tablets are included in the Abergic line of tablets which are formulated to contain excipients, diluents and granulating substances, such as arrowroot starch, cane sugar, and talc, that are less likely to cause allergic reactions than corn starch, lactose and tragacanth, commonly used in tablet manufacture.

One hundred milligrams was found to be the average adult dose, although 50 mg. usually served to control the milder symptoms. For children, the syrup was used and one-half to one teaspoonful according to age was found sufficient. Relief was obtained in twenty to thirty minutes when given orally and lasted from three to four hours. Children five and six years old tolerated teaspoonful doses of the syrup without untoward effect. Of the entire series of 175 patients only two experienced unpleasant effects of nausea and vomiting. Patients were instructed to take the drug when symptoms first were manifest with the exception of the asthmatics who were instructed to take it prophylactically. Only those who followed instructions to omit the so-called antihistamines and sedatives are included in this report. If symptoms became worse, a subcutaneous injection of epinephrine was given and the case was considered a "poor" result.

The majority of patients were receiving specific immunization therapy and all were told that the drug was given to obtain symptomatic relief when necessary. Results were noted by questioning the patients when they reported every five days for their antigen injections; otherwise by telephone or on their next visit.

Results are listed in Table I.

TABLE I. RESULTS OF TREATMENT OF 175 PATIENTS WITH ORTHOXINE

	Results		
Allergic Rhinitis	*Good*	*Fair*	*Poor*
Perennial	5	10	3
Seasonal	30	15	10
Asthma			
Mild	11	6	3
Severe	3	3	7
Urticaria			
Acute (frequent dosage)	14	4	2
Chronic	1	7	7
Angioneurotic Edema	2	3	1
Atopic Dermatitis (relief of pruritus)	0	8	8
Allergic Headaches (Including Migraine-large doses given early and frequently)	6	3	1
Obstructive Emphysema (Allergic Bronchitis)	1	1	0
Total	73	60	42

COMMENT

Compared with a large series of cases previously treated with ephedrine, those receiving Orthoxine showed a heart rate which was more regular and stronger. Also, no arrhythmias were noted as were occasionally produced by ephedrine. No increase of blood pressure was noted in those receiving Orthoxine, even in the arteriosclerotic patients—in fact, an occasional transient depressor response was noted with flushing in three patients. More favorable results were noted in the mild asthmatic patient than in the seasonal hay fever cases. Five of nine severe asthmatic patients were relieved by 50-100 mg. every three hours. No ill effects were noted when continuing these doses. Results were superior in all cases

to those obtained with ephedrine alone. The absence of nervousness and pressor effects was notably absent.

Gastrointestinal allergy was often alleviated, apparently by relieving smooth muscle spasm. One patient with cardiospasm obtained satisfactory relief by taking 50 mg. one-half hour before eating.

Orthoxine in 100 mg. doses every three hours aborted about two-thirds of allergic headache if taken early. Two cases of migraine were followed by nausea and vomiting. As in asthma, little or no relief was obtained if the attacks were well developed.

SUMMARY

Orthoxine, like ephedrine, has advantages over ephedrine in that it is not affected by digestion and may be given orally. Its greatest value is as a preventive, and its action is just as prolonged as that of ephedrine. It also possesses the advantage of not causing the unpleasant effects of nervousness and other central nervous system excitatory effects, as well as no distressing pressor symptoms. It is safer to give in the old age group.

The greatest benefits, however, were obtained when used in conjunction with avoidance and immunization measures. When administered in 50 mg. doses one-half hour before a high dose of pollen or inhalant extract, it would permit a higher tolerance dose and compared favorably to the antihistaminic drugs in this respect.

Controls using a combination of Orthoxine with barbiturates of either the short or long acting types gave more satisfactory results than when Orthoxine was administered alone. Such a combination gave considerably better results, but these results are not included in this report since the comparative effect of this synthetic amine with ephedrine alone was desired. Other combinations which have so far given very promising superior results are Orthoxine and a theophylline derivative in combination with an antihistamine and Orthoxine, theophylline derivative, and phenobarbital. Orthoxine alone has been found to be a valuable aid in the treatment of those allergic diseases benefited by ephedrine, with the advantage of being comparatively free from side reactions.

REFERENCES

1. Abel, J. J., and Crawford, H. C.: Bull. Johns Hopkins Hosp., 8:151, 1897.
2. Aldrich, T. B.: J. Am. Chem. Soc., 27:1074, 1905.
3. Barger, G., and Dale, H. H.: J. Physiol., 41:19, 1910.
4. Swanson, E. E., and Webster, R. K.: J. Pharm. & Exp. Therap., 38:327, 1930.
5. Takamine, J.: Therapeutic Gazette, 27:221, 1901.
6. Von Furth, O.: Ztschr., J. Physiol. Chem., 29:105, 1900.

CRYMOTHERAPY AND ANAPHYLAXIS

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TEMPLE Fay[1] and his associates in studying refrigeration of humans have shown that the body temperature may be lowered to 31° C. for as long as eight days. The lowest temperature induced by Fay in a human was 23.3° C. Death ensued after four hours. Whittemore[5] and his group, in studying the refrigeration problem in animals, found the respiratory exchange is lowered in hibernating animals, and below 15.5° C. the respiratory quotient may be reduced to as low as 0.51. Similar changes in humans have not been found. In hibernating animals the blood sugar and adrenalin were decreased. In humans under refrigeration there are no significant changes in blood urea, nonprotein nitrogen, cholesterol, sugar, chlorides, calcium, phosphorus, or CO_2 combining power. A significant observation in hibernating animals was the definite lowering of the basal metabolic rate. In refrigerated humans a lowering of the basal metabolic rate was also observed.

The observations of a decreased metabolism suggested that various undetermined physiologic processes were slowed up, if not actually suspended. It occurred to the author that use of refrigeration might possibly slow up or suspend the antigen-antibody reaction of anaphylaxis or possibly affect the action of histamine on the bronchial musculature of guinea pigs. Two interesting experiments sustained these possibilities. Taintor is quoted by Whittemore as having found that toxic dinitrophenol injected into guinea pigs and pigeons failed to produce the usual stimulation if environmental temperature was 38° to 42° F., and only 25 per cent of the birds died. Toshivo Akiyama is also mentioned by Whittemore as having inoculated ground squirrels with the virus of lymphogranuloma inguinale and then put them into hibernation. Those which hibernated for twenty days remained unharmed without signs of the disease. The controls, not hibernated, died.

Twenty guinea pigs of average 300 gm. weight were sensitized by an intra-abdominal injection of 1 c.c. of a 1:10 dilution of horse serum. After fourteen days, the animals were refrigerated. Since this was in the nature of a preliminary experiment, a simple technique of tying down the four limbs of an animal to a base board and packing ice about it was used. A thermometer was kept fixed in the rectum of each animal. Temperatures dropped from 38° C. to 25° C. within a matter of thirty minutes. No anesthetic to make induction of refrigeration easier was used. Since the room temperature usually ranged from 14° to 20° C., when the induced temperature reached 25° C., the ice was removed from the guinea pigs. Their temperatures drifted slowly downward, and often it was necessary to reheat the animals to prevent it from falling too low.

Of the twenty animals thus refrigerated, seven died from the procedure

because the temperature had been deliberately lowered dangerously to between 16° and 20° C., with the intention of observing the effects of extremely low temperatures. It may be stated that at 25° C. the animal may easily be restored, by reheating with a heating pad, and returned to normal life. Autopsy findings on animals dying from lowered temperatures revealed that refrigeration induced extreme distention of the entire gastrointestinal tract, including the gall bladder. The liver was also enormously enlarged and showed passive congestion. The lungs were small and pink, except in those cases refrigerated for several hours, in which passive congestion was present with isolated hemorrhagic areas on the surface. The auricles and tributary veins were moderately engorged. The over-all heart size seemed normal.

The actual test animals were refrigerated at temperatures ranging from 18° to 27° C. for periods varying from sixty to 195 minutes, after which time they received an intravenous injection of 1 c.c. of a 1:2 dilution of horse serum. Of the thirteen animals who survived refrigeration, only five survived fatal anaphylactic shock, and all of these animals showed signs of anaphylaxis. Fatal shock was confirmed by autopsy findings. Due to the relatively inactive condition of the animals under refrigeration, the only dependable sign of anaphylaxis was severe dyspnea. Shivering, followed by clonic-like movements of the limbs and accompanied by rapid, shallow breathing, was observed during the process of refrigeration. Ten control animals, not refrigerated, died from fatal anaphylaxis after the same shock dose.

Refrigeration seemed to produce an unsual condition in guinea pigs, with respect to anaphylaxis, which neither histaminase, histamine, papaverine nor crotalin[2,3,4] had produced. It definitely seemed to lengthen the time interval between the injection of the shock dose of antigen and the onset of anaphylactic dyspnea. This retarding of the effects of the immunological reaction could have taken place at several possible points. The circulation time might have been slowed so that the antigen reached the site of the shock organ slowly; or the reaction between antigen and antibody might have been slowed; or after the said reaction, the release of histamine from the cells might have been slowed; or, lastly, the action of released histamine on bronchial musculature might have been delayed. Thus far, it has been convenient to test only one of these possibilities, the last. For this, five guinea pigs, refrigerated from sixty to 200 minutes, were injected intravenously with histamine in a dose of .045 mg. per 100 gm. weight. All five died in shock but after a lapse of six to nine and one-half minutes. Signs of dyspnea were delayed three to five minutes in starting. In fatal histamine shock, dyspnea sets in usually in fifteen to sixty seconds. The delay in onset of symptoms due to the action of histamine seems significant and is apparently attributable to the slowing of some physiological processes as a result of refrigeration.

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THE INTEGRATION OF THE PRACTICE OF ALLERGY AND PSYCHIATRY

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PSYCHOSOMATIC medicine has become of increasing interest and importance in the past few years, as evidenced by the vast literature and by the popularity of symposia on this subject.

Recently, The American College of Allergists conducted a forum on "Psychodynamics and the Allergic Patient."* indicating the progress made in both fields—the allergist becoming aware of the importance of the psychiatric approach to some of his problems, and the psychiatrist in turn coming around to the view that, although he could be of help to the allergist, allergy was not *exclusively* within his domain. In the past, it is to be regretted, some rash psychiatrists had expounded views indicating that asthma, hay fever, urticaria, and other allergic diseases were primarily psychosomatic disorders, denying hypersensitivity, the basis of allergy. Now we are agreed that both the allergist and the psychiatrist can jointly contribute to the solution of some problems seen by the allergist.

Allergy and psychiatry have a great deal in common. Both are new disciplines in the practice of medicine, and as such are not completely accepted in certain medical circles who deny the role of either allergens or emotions in the production of disease.

Both the allergist and psychiatrist are essentially medical detectives; they search for hidden causes. The allergist looks for specific allergens and resorts to his special techniques of skin-testing, food diaries, elimination diets, et cetera. The psychiatrist probes the unconscious mind with his special technique of psychoanalysis in order to uncover hidden emotional factors producing symptoms.

The two disciplines treat primarily with disturbances in *function* although organic disease is encompassed within the boundaries of both allergy and psychiatry. The underlying mechanism in an allergic reaction, according to present theory, is based on a specific antigen-antibody reaction, resulting in the release of histamine or a histamine-like substance in a hypersensitive individual. Comparably, emotional disorder, according to Freudian concepts, is produced between the interaction of the Ego and the Id in a susceptible individual, and may manifest itself in organ reaction, producing symptoms.

In allergy, the skin is frequently the "bookkeeper of the body," record-

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Based upon an address delivered as part of a symposium on psychosomatic medicine, held under the auspices of the Department of Psychiatry, New York Medical College, Flower-Fifth Avenue Hospital, New York, N. Y., June 12. 1947.

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*Third annual session, the American College of Allergists, June 7, 1947, Atlantic City, N. J.

ing experiences (exposures to specific allergens) of the past. It records sensitivity which may have been acquired years ago and which may be revealed by skin-testing. This is comparable to the indelible recording of certain emotional experiences within the recesses of the unconscious mind—experiences which, considerably later, may generate symptoms. There is a type of "sensitization" in both instances. Embryologically, it must be recalled, the skin and brain have a common origin, the ectoderm.

Another phenomenon common to allergy and psychiatry is that exposure to relatively innocuous substances or situations may result in explosive reactions in these "sensitized" individuals. Thus, the anaphylactic type of reaction which may follow the ingestion of milk or aspirin may be comparable to the induction of an acute psychosis by some mild mental trauma or frustration. A fertile field or "sensitivity" is necessary in both instances. Sometimes, these reactions are mild but continuous, resulting in chronic irritation and disability. At times, the reaction is delayed following exposure, a period of "incubation" being needed before the production of mental or allergic symptoms. At other times, an initial exposure to a harmful allergen or experience results in a series of "chain reactions"—an imbalance is created which may enhance and multiply the "sensitivities" of the allergic or psychiatric patient.

In the therapeutic approach to the patient, there is much in common between the allergist and the psychiatrist. We both seek "cures" by searching for and removing specific offenders, whether it be a specific allergen in the form of a cat or canary, or a specific fixed idea or situation causing emotional disturbances. Failing such "cures," we both resort to "desensitization"—the allergist by injection with specific antigens, and the psychiatrist by psychotherapy.

The fact that the emotions can produce symptoms, often mistaken for organic disease, is now generally accepted, and we must be grateful to those keen observers (internists and psychiatrists) who have reawakened our interest in an old subject, newly named psychosomatic medicine.

Undoubtedly, the allergist can learn much from the psychiatrist, who is a specialist in the art of history-taking. An accurate and detailed history can be more important to the allergist than skin-testing. Furthermore, the emphasis of psychiatry upon the consideration of the *individual as a whole* in a *specific environment* (as though he were bathed in a sea of stimuli, emotional and otherwise) merits emulation by the allergist. Without such a broad consideration, one treats symptoms out of context, a narrow and limited view frequently leading to failure. In the opinion of Nardo,† such a limited view results in the practice of "veterinary medicine."

The allergist might heed as well the injunction of Weiss†: "to consider not only what the patient 'et' but whom he may have met."

The allergist is aware of the fact that asthma itself, regardless of

†Discussion of Harold A. Abramson's paper on: "Psychodynamics and the Allergic Patient."

cause, may produce a neurosis in the patient. The sufferer from asthma, during an attack, frequently fears impending death and develops phobias as a result of this experience. This has been labeled by Sarah Jordan as a "somatopsychic" manifestation in contrast to psychosomatic phenomena. What the allergist frequently overlooks, however, is the fact that once asthma supervenes, though it may have been strictly allergic in origin, it may *recur* on a psychogenic basis. Thus, the youngster who has asthma from the ingestion of specific foods may precipitate an attack just before leaving for school because he does not like his teacher, or because he wants (and needs!) the attention of an errant mother. Failure of the allergist to recognize this aspect of his practice will result in failure of therapy, regardless of dietary restrictions, environmental cleansing, and injections. The allergist should be cautioned, however, of the danger of so emphasizing the psychogenic factors as to overlook completely the cat or canary, whose removal may relieve the patient.

When the allergist is aware of the psychosomatic aspect of illness, he is frequently uncertain as to when the psychiatrist need be consulted. Moreover, when he does feel the need for psychiatric help, he is often deterred from such consultation because of the prohibitive cost in both time and money—assuming he has convinced the patient of the advisability of such a procedure, which is frequently an impossibility.

It, therefore, behooves the psychiatrist to teach us to recognize psychogenic factors, to determine when the special techniques of psychiatry are indicated and, above all, to simplify and shorten the methods of analysis and therapy so that it comes within the bounds of the average patient.

When the allergist and the psychiatrist forget the "either or" concept and, instead of being at loggerheads, join co-operatively to treat patients, then progress will surely have been made—to the benefit of both doctor and patient.

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Dr. Bernard N. Halpern, Paris, France, the Lauréat of the Institute and Academie of Medicine, Chief of Laboratories of the Faculté of Medicine and Chief of Research of the National Center of Scientific Research, has joined the Editorial Board of the *International Archives of Allergy and Applied Immunology*, the official organ of the International Association of Allergists, Inc.

RELIEF OF ASTHMA BY MEANS OF LOW MELTING POINT SUPPOSITORIES

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AN asthmatic suffering from an acute paroxysm desires speedy relief. In proven cases, the self-administration of certain drugs such as 1:100 epinephrine hydrochloride, glycerinized or unglycerinized, via oral inhalation; the use of ephedrine or aminophylline, et cetera, orally, and the use of aminophylline in solution or aminophylline suppositories intrarectally can safely be recommended.

Aminophylline is rapidly absorbed from the mucosa of the lower intestine through the portal system. If the drug is given in solution according to the method described by Barach,[2] absorption takes place rapidly. Relaxation of the smooth muscles of the bronchi takes place, and, in most instances, the patient secures the desired relief.

The use of aminophylline hypodermically or by catheter usually requires the presence of a physician or nurse. Suppositories containing aminophylline in combination with other drugs can easily be self-administered.

Practically all of the commercial aminophylline suppositories in use at the present time have a base with a high melting point. This delays absorption of the drugs incorporated in the suppository base. Bowel movements are often produced by the pressure and hydroscopic action of the suppository in the rectum.

A burning and painful sensation is also produced when aminophylline suppositories are used, even though various local anesthetics are incorporated into the base of the suppositories.

During the 1945 Fall Instructional Course of the American College of Allergists,[1] the formulas of a number of low melting point suppositories that have been in use at the Lancaster General Hospital during the last five years were submitted and are listed as follows:

No. 1

Aminophyllin gr. vi
Ephedrine sulphate gr. 3/8
Phenobarbital gr. i
Nupercaine qs. 1 per cent
Peanut oil, spermaceti and oleum theobromitas in equal parts to make one suppository.

No. 2

Aminophyllin gr. vi
Sodium Pentobarbital gr. iii
Nupercaine qs. 1 per cent
Peanut oil, spermaceti and oleum theobromitas in equal parts to make one suppository.

Presented at the annual meeting of The American College of Allergists, Atlantic City, New Jersey, June 7, 1947.

No. 3

Aminophyllin gr. vi
Ephedrine sulphate gr. ss
Sodium Pentobarbital gr. iss
Nupercaine qs. 1 per cent
Peanut oil, spermaceti and oleum theobromitas qs. one suppository.

No. 4

Aminophyllin gr. vi
Ephedrine sulphate gr. ss
Demerol, 50 milligrams
No anesthetic
Peanut oil, spermaceti and oleum theobromitas to make one suppository.

The suppository base used in the formulas was originated by two Lancaster pharmacists.* Only two cases in which an untoward reaction had been produced by the use of one of the suppositories have been noted.

CASE REPORTS

Case 1.—Sister E. A., a nun, aged twenty-six, a hay-fever sufferer and pollen asthmatic, was given the following prescription:

Aminophyllin gr. vi
Sodium Pentobarbital gr. iss
Nupercaine qs. 1 per cent
Peanut oil, spermaceti and oleum theobromitas qs. one suppository.
Misce: XII suppositories.
Signa: Insert one into rectum before retiring for relief of nocturnal attacks.

Sister E. developed a rather severe edema of the anal area plus severe itching after the use of one of these suppositories. She later was proved to be sensitive to coca butter.

Case 2.—Another patient developed a generalized urticaria after using several of the following suppositories:

Aminophyllin gr. vi
Ephedrine sulphate gr. ss
Sodium Pentobarbital gr. iss
Nupercaine qs. 1 per cent
Peanut oil, spermaceti and oleum theobromitas qs. one suppository.

The cause of the urticaria was not determined since the patient did not return for testing. One of the following ingredients was probably responsible: peanut oil, coca butter, nupercaine or sodium pentobarbital. No one sensitive to spermaceti has been discovered by the writer. As far as is known, none have been described or listed in the pertinent literature.

The loss of popularity of medications administered via suppositories can be attributed to three factors:

1. Lack of certainty with regard to dosage.
2. Slow absorption due to high melting point base.
3. Allergy to the base.

Since the suitability of the mucous surface of the bowel for prompt absorption of the drugs has been well established,[4,5] the marked decrease in effectiveness of drugs so administered must be due to the influence of the suppository base, or to a sensitivity to one of the ingredients in the base of the medications incorporated therein. The need for a sup-

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pository base which would not contain coca butter or peanut oil and still have a low melting point has been known for some time.

Data from recent studies indicate that fatty bases have a deleterious influence on absorption and availability of both oil and water soluble drugs.[3,4] This may be overcome by the addition of a suitable emulsifying agent.

Spermaceti was selected with these facts in mind. It consists chiefly of cetyl palmitate, cetyl alcohol in appreciable amounts and small amounts of the esters of lauric acid, stearic and myristic acids. Cetyl alcohol itself is a good emulsifying agent.

The melting point of spermaceti is 42° to 50° C. The addition of liquid petrolatum and white petrolatum to lower the melting point and still leave a solid medication was undertaken. The following is the finished suppository base:

Petrolatum liquid	42.
Spermaceti	45.
Petrolatum alba	13.
	100.

If a more solid medium with a slightly higher melting point is desired, it can be obtained by increasing the amount of spermaceti and by decreasing the amounts of petrolatum. The formulas in use at the present are made as follows:

No. 1

Aminophyllin gr. vi
Ephedrine sulphate gr. 3/8
Phenobarbital gr. i
Nupercaine qs. 1 per cent
Base qs. one suppository.

No. 2

Aminophyllin gr. vi
Sodium Pentobarbital gr. iss to gr. iii
Nupercaine qs. 1 per cent
Base qs. one suppository.

No. 3

Aminophyllin gr. vi
Ephedrine sulphate gr. ss
Sodium Pentobarbital gr. iss
Nupercaine qs. 1 per cent
Base qs. one suppository.

No. 4

Aminophyllin gr. vi
Ephedrine sulphate gr. ss
Demerol, 50 milligrams
Base qs. one suppository.

The base melts rapidly at body temperature, and the absorption of the drugs incorporated therein takes place rapidly. Self-administration of the suppository can safely be recommended. They can be used to control attacks of asthma, to relieve nocturnal attacks and to provide the relaxation that an asthmatic patient requires to secure an adequate amount of sleep.

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ASYMPTOMATIC EOSINOPHILIA FOLLOWING PENICILLIN ADMINISTRATION

Report of a Case

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ALTHOUGH reactions to crystalline penicillin of allergic nature have been frequently reported since this drug first came into common therapeutic use,[9,11,13] the presence of eosinophilia has only infrequently been noted to accompany such reactions.[4,12,13] Eosinophilia without any other manifestation of hypersensitivity to penicillin has never been previously noted in the literature, however. This prompted the report of such a case.

CASE REPORT

E. L., a seventy-three-year-old white widowed woman entered the hospital on May 30, 1946. She had been apparently in subjective good health until one week prior to admission, when pain was noted in the right upper quadrant of the abdomen, radiating to the tip of the right shoulder and aggravated by cough and deep breathing. Following this, the patient became weak, listless and anorexic, and vomited green material on several occasions. Because of persistence of symptoms, admission to the hospital was sought. Past and family histories were noncontributory.

Physical examination revealed an obese, elderly, white woman lying semi-recumbent in bed and breathing dyspneically. Temperature was 100° by mouth, pulse 96, and respiration 32 per minute. Neck veins were moderately distended. The heart was enlarged 2 cm. to the left of the mid-clavicular line. Rhythm was regular, and the rate was 96. A rough, grade 2, aortic systolic murmur, transmitted to the cardiac apex and into the neck, was audible. Examination of the lungs revealed moderate dullness, bronchovesicular breath sounds and crepitant râles at the right lung base. Medium moist râles were present at the left lung base. Blood pressure was 140/80. The physical examination was othewise negative, with the abdomen revealing no abnormal masses or tenderness. X-ray examination of the chest revealed marked cardiac enlargement, hypertensive in type, with calcification of the aortic arch and bilateral congestive changes. At the right lung base there was an area of infiltration, and fluid was present in the septum between the right middle and lower lobes. Therapy consisted of digitalization and crystalline sodium penicillin, the latter in doses of 20,000 units every three hours. The white blood count was 7,200, with 76 per cent segmented neutrophiles and 24 per cent lymphocytes.

On the second hospital day, the patient's temperature rose to 102.4° F. by mouth, and because of continued nausea and occasional vomiting, subcutaneous clyses were begun. During the following day, however, the patient began to improve gradually. Her temperature gradually diminished until the eighth hospital day, when it reached normal. Two days later, however, the patient again became dyspneic and her temperature rose to 101.5° F. by mouth. Examination of the chest at that time revealed flatness and markedly diminished to absent breath sounds at the right lung base. An x-ray taken at that time revealed homogeneous obliteration of the right lower lung field, interpreted as fluid. Thoracentesis yielded 500 c.c. of cloudy straw-colored fluid, which clotted shortly after withdrawal and

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had a specific gravity of 1.018. Crystalline sodium penicillin, 60,000 units in 20 c.c. of saline, were instilled at the site of the thoracentesis. Cultures of the fluid were negative as was the guinea pig inoculation. Thoracentesis was repeated one week later, but only 20 c.c. of fluid were obtained; 60,000 units of penicillin were again instilled at the site of the thoracentesis.

On continued intramuscular penicillin therapy, the patient's temperature continued elevated for the following three weeks, and she continued anorexic and moderately dyspneic. The white blood count (June 24) was 5,300, with 85 per cent neutrophiles and 15 per cent lymphocytes. Early in July, five weeks after entry, the patient's temperature gradually fell to normal, where it remained throughout the remainder of her hospital stay. Despite reversion of the temperature to normal, a dullness to flatness, with markedly diminished breath sounds, continued at the right base. On July 25, 1946, eight weeks after admission the white blood count was noted to be 14,500, with 52 per cent neutrophiles, 30 per cent lymphocytes and 18 per cent eosinophiles. On the following day, differential white blood count revealed 28 per cent eosinophiles, and a total eosinophile count was 1,890 per cubic millimeter. At this point the penicillin was discontinued, and one week later the white count was 6,300, with 4 per cent eosinophiles. At this time stool examinations revealed no ova or parasites, and a trichina skin test was negative. Other medications being administered at the time were digitalis, niacinamide, cevitamic acid, Brewer's yeast, and thiamine hydrochloride.

Three days after the reversion of the white blood count to normal, on August 5, the patient was again given 20,000 units of crystalline sodium penicillin every three hours intramuscularly for a period of three days. The white blood count on August 6 was 8,400, with 3 per cent eosinophiles, and on August 8 it was 12,000, with 1 per cent eosinophiles. On August 11, six days after penicillin had been recommenced, and three days after it had been discontinued for the second time, the white blood count was 9,500, with 14 per cent eosinophiles. Total eosinophile count at this time was 1,710 per cubic millimeter. The eosinophile count then fell gradually until August 21, when it was 2 per cent of 8,200 white blood cells. At this time an intradermal skin test with 0.1 c.c. of sodium penicillin, 10,000 units per c.c., gave a positive tuberculin-type reaction which appeared in twenty-four hours and faded in one week. On October 10, 1946, shortly before discharge from the hospital, the patient was given 10,000 units of crystalline sodium penicillin intramuscularly four times daily. On commencing penicillin administration, the white blood count was 8,500, with 1 per cent eosinophiles. Two days later, it was 9,200 with 21 per cent eosinophiles. Eight days after penicillin had been discontinued, the white blood count was 8,000 with 6 per cent eosinophiles. At no time during any course of penicillin administration did the patient show skin lesions of any type. Different lots of penicillin were used throughout the testing, thereby eliminating the factor of a common contaminant in the drug.

DISCUSSION

The case reported first developed an eosinophilia following eight weeks of almost constant intramuscular administration of crystalline sodium penicillin. Other common causes for eosinophilia could not be found, and one week after the withdrawal of penicillin the eosinophile count had reverted to normal. Later in the patient's hospital stay, the eosinophilia was reproduced on two occasions. The first was six days following the administration of 20,000 units of crystalline sodium penicillin every three hours. The second reproduction of eosinophilia occurred two days following the intramuscular administration of 10,000 units of penicillin four

times daily. An intracutaneous skin test with crystalline sodium penicillin gave a positive tuberculin-type skin reaction in twenty-four hours, with fading in one week.

In 1943, Lyons[10] noted that eosinophilia of 20 to 30 per cent often occurred following the use of penicillin. At that time it was felt that most of these reactions were probably due to impurities and could be prevented by Seitz filtration of the solution before injection. Since crystalline sodium penicillin has come into common use, there have been only a few other reports of a significant eosinophilia following penicillin administration.[4,12,13] It thus seemed that Lyon's assumption of impurities as the cause of the occurrence of eosinophilia in the high percentages he noted, was, for the most part, true. However, during the past year, reports of eosinophilia accompanying other manifestations of hypersensitivity due to crystalline penicillin have appeared with increasing frequency. Almost all occur in combination with skin lesions. These allergic phenomena have varied from mild skin reactions to severe cases of bullous dermatitis.

The reactions of patients to penicillin have been studied by numerous investigators. Criep[5] demonstrated positive direct and passive transfer tests to penicillin in a patient who developed urticaria following the first injection in a second course of treatment. He concluded that the sensitivity was due to penicillin itself rather than to any contaminating impurities. Lamb[9] believes that the allergenic principle in penicillin is in all probability a polysaccharide fraction. He quotes Jadassohn, Schaaf, and Sulzberger,[8] who found that the products of fungi could produce anaphylactic shock in guinea pigs. These observers also noted that pathogenic fungi contain not only a specific antigen but also another antigen common to all fungi. Price[14] feels that hypersensitivity to penicillin requires an allergen other than penicillin alone. He presumes that the patient's own serum provides the necessary protein. Welch and Rostenberg[18] demonstrated an intense tuberculin-type reaction from intracutaneous tests with penicillin. They state that approximately 5 per cent of 140 previously unexposed persons exhibited a tuberculin-type reaction to the initial injection of crystalline sodium penicillin. Cormia, Jacobsen, and Smith[4] feel that such reactions stem from previous sensitivity to allergenically similar fungi. Feinberg[6] is of similar opinion, stating that early reactions to a first exposure to penicillin are probably due to previous fungus disease, whereas delayed reactions are indications of sensitization development which also may be enhanced by previous fungus disease.

The presence of eosinophiles in increased numbers in the blood stream has been reviewed by Stickney and Heck.[17] These authors note that most experimental studies on the origin of the eosinophilia or the granules of the eosinophilic leukocyte point to the importance of anaphylaxis. Eosinophilia is a common finding in (1) asthma, hay fever and vasomotor rhinitis; (2) parasitic infection, particularly of the intestines; (3)

dermatoses, especially of the allergic type, and (4) blood dyscrasias and lymphoblastoma. To these causes may be added the administration of medications such as atabrine[16] and liver extract,[7] and less common entities such as Loeffler's syndrome and periarteritis nodosa.

The possible relationship of the eosinophile to blood histamine content and the clinical signs of allergy has been a controversial point. Code[1,2] found that the white cell layer in sedimented blood contained almost 90 per cent of the histamine content of the whole blood when compared with plasma and red cells. During anaphylactic shock, this observer found that the histamine values rose three to nine times in shocked animals, the escape of histamine taking place in the white cell, chiefly from the eosinophiles. He, therefore, concluded[3] that histamine released during anaphylactic shock was an important factor in producing the symptoms and pathologic changes in the reaction. Randolph and Rackeman[15] likewise noted that during paroxysms of bronchial asthma in a group of nine cases, elevated blood histamine levels occurred, as compared with quiescent periods. However, they found that in another series of eight cases of eosinophilia of varying etiology, only two cases had elevated blood histamine values. From these studies, it would appear that blood histamine undergoes a definite increase during acute manifestations of hypersensitivity, but that the relationship of blood eosinophiles to histamine is as yet unproven although suggestive.

Thus, the finding of isolated, reproducible eosinophilia in this case is in all probability a manifestation of allergy to crystalline sodium penicillin.

SUMMARY

1. A case of asymptomatic eosinophilia due to the administration of crystalline sodium penicillin is presented.

2. The eosinophilia occurred after continuous administration of the drug over an eight-week period. Following discontinuance of the drug, the eosinophilia disappeared, but it was later reproduced on two occasions by administering penicillin for short courses.

3. Intracutaneous administration of a solution of crystalline sodium penicillin caused a tuberculin-type reaction.

4. The relation of penicillin reactions to hypersensitivity is discussed, as is that of eosinophilia and hypersensitivity.

REFERENCES

1. Code, C. F.: The source in blood of the histamine-like constituent. J. Physiol., 90:349, 1937.
2. Code, C. F.: The histamine-like activity of white blood cells. J. Physiol., 90:485, 1937.
3. Code, C. F.: The mechanism of anaphylactic and allergic reactions; evaluation of the role of histamine in their production. Ann. Allergy, 2:457, 1944.
4. Cormia, F. F., Jacobsen, L. Y., and Smith, E. L.: Reactions to penicillin. Bull. U. S. Army M. Dept., 4:694, 1945.
5. Criep, L. H.: Allergy to penicillin. J.A.M.A., 126: 429, 1944.

6. Feinberg, S. M.: Penicillin allergy; on the probability of allergic reactions in fungus-sensitive individuals. J. Allergy, 15:271, 1944.
7. Hanno, H. A., and Munsh, M.: Eosinophilia following parenteral liver therapy. Am. J. Med. Sc., 209:572, 1945.
8. Jadassohn, W., Schaaf, F., and Sulzberger, M. B.: Der Schultz-Dalesche Versuch mit Trichophyton. Klin. Wchnschr., 11:857, 1932.
9. Lamb, J. H.: Allergic reactions during the administration of penicillin. Arch. Dermat. & Syph., 52:93, 1945.
10. Lyons, C.: Penicillin therapy of surgical infections in the U. S. Army. J.A.M.A., 123:1007, 1943.
11. Macey, H. B., and Hays, T. G.: Allergic reactions to penicillin therapy. U. S. Navy M. Bull., 45:1143, 1945.
12. Morginson, J. W.: Toxic reactions accompanying penicillin therapy. J.A.M.A., 132:915, 1946.
13. Mendell, T. H., and Prose, P. H.: Severe allergic reactions to penicillin. Am. J. Med. Sc., 212:541, 1946.
14. Price, I. C.: Severe allergic reaction to intramuscular penicillin. Canad. M.A.J., 53:485, 1946.
15. Randolph, T. G., and Rackemann, F. M.: Blood histamine levels in asthma and in eosinophilia. J. Allergy, 12:450, 1941.
16. Russell, H. K.: Eosinophilia caused by atabrine. U. S. Nav. M. Bull., 44:574, 1945.
17. Stickney, J. M., and Heck, F. J.: Clinical occurrence of eosinophilia. M. Clin. North America, 28:915, 1944.
18. Welch, H., and Rostenberg, A., Jr.: Hypersensitivity of the tuberculin type to crystalline penicillin sodium. J.A.M.A., 126:10, 1944.

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THE TOPICAL APPLICATION OF THEPHORIN IN PRURITIC DERMATOSES

(Continued from Page 644)

REFERENCES

1. Bishop, G. H.: The skin as an organ of sense with special reference to the itching sensation. J. Invest. Dermat., 11:143, (Aug.) 1948.
2. Dragstedt, C. A., and Mead, F. B.: The role of histamine in canine anaphylactic shock. J. Pharmacol. & Exper. Therap., 57:419, (Nov.) 1932.
3. Feinberg, S. M., and Bernstein, T. B.: Triplennamine "Pyribenzamine" ointment for the relief of itching. J.A.M.A., 134:874, (July 5) 1947.
4. Fourneau, E., and Bovet, D.: Recherches sur l'action sympathicolytique d'un nouveau derive du dioxane. Arch. Internat. de Pharmacodyn. et de Therap., 46:178, (Oct. 15) 1933.
5. Friedlaender, S., and Feinberg, S. M.: III Histamine anatgonists. The effect of oral and local use of beta-dimethylaminoethyl Benzhydryl ether hydrochloride on the whealing due to histamine. Antigen antibody reactions, and other whealing mechanisms. Therapeutic results in allergic manifestations. J. Allergy, 17:129, (May) 1946.
6. Leavitt, M. D., and Code, C. F.: Anesthetic action of beta-dimethylaminoethyl Benzhydryl ether hydrochloride (Benadryl) in skin of human beings. Proc. Soc. Exp. Biol. & Med., 65:33, 1947.
7. Lehmann, G.: Pharmacological properties of a new antihistaminic, 2-methyl-9-phenyl-2, 3, 4, 9-tetrahydro-1-pyridindene (Thephorin) and derivatives. J. Pharmacol. & Exp. Therap., 62:249, (March) 1948.
8. Mayer, R. L.: Pyribenzamine in experimental non-allergic and allergic dermatitis. J. Invest. Dermat., 8:67, (Feb.) 1947.
9. Perry, D. J.: The local use of Benadryl ointment. J. Invest. Dermat., 9:95, (Aug.) 1947.
10. Sulzberger, M. B., and Baer, R. L.: Editorial Comment, Yearbook of Dermatology and Syphilology. Chicago: Yearbook Publishers, 1947.
11. Wooldridge, W. E., and Joseph, H. L.: Thephorin in the treatment of disseminated neurodermatitis. J. Invest. Dermat., 11:93, (Aug.) 1948.

DERMATITIS CAUSED BY ELECTRODE JELLY

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THIS is a case report of dermatitis caused by electrode jelly. To my knowledge this is the first case to be reported. That this condition is rare is proven by the fact that at the Electrocardiography Department of the Veterans Administration Hospital at Hines, Illinois, where about 14,000 electrocardiographic examinations were performed during the past twelve months, no known sensitivity to the jelly was reported.

CASE REPORT

In January, 1943, while R. C., a white man, aged forty-two, was hospitalized in the Canadian Naval Hospital in St. John, N. F., an electrocardiogram was done. Shortly after the examination, he noticed a redness with slight swelling at the site of the application of the electrode jelly. Within twenty-four hours a pinpoint rash appeared at the sites, the swelling increased, and in two days the areas assumed a hemorrhagic appearance. The rash gradually dried up and disappeared within twenty-five to thirty days without any desquamation.

On February 28, 1947, he was called to the Veterans Administration Out-Patient Department for an examination and electrocardiogram. At the completion of the test a rash again appeared at the site of the application of the electrode jelly.

Examination of the rash at that time revealed a finely papular erythematous patch of irregular outline on both forearms (Fig. 1). There was a profusion of discrete, pinhead-sized, pale erythematous papules on the volar aspects of both forearms from the antecubital areas to the wrists, and a moderate number on the anteromedial aspect of the proximal half of the lower half of the left leg (Fig. 2). There was also a profusion of discrete pinhead, erythematous papules over an area of about 6 inches square on the left chest (Fig. 3).

Within forty-eight hours these areas assumed a hemorrhagic petichial appearance and were accompanied by intense itching. Within about twenty-one days the rash gradually faded and disappeared without any scarification.

On June 25, 1947, vigorous rubbing of small amounts of two types of electrode jelly used at the out-patient department, into small areas of each forearm, produced the same rash.

Scratch tests performed with the individual ingredients of the electrode jelly gave the following results:

Oil of pine needles—negative.
Sodium benzoate—negative.
Sulfonated castor oil—negative.
Potassium bitartarate—negative.
Gum tragacanth—2-plus.
Glycerine—negative.
Powdered pumice—negative.
Sodium chloride—negative.

A patch test with the gum tragacanth gave a positive reaction within twenty-four hours, and the resulting rash had the identical characteristics of the one obtained by the jelly.

Control tests on known allergic and nonallergic individuals with the same ingredients, did not elicit any positive skin reactions.

From the Department of Medicine, Veterans Administration, Regional Office, Out-Patient Department, and from the Department of Internal Medicine, Northwestern University Medical School.

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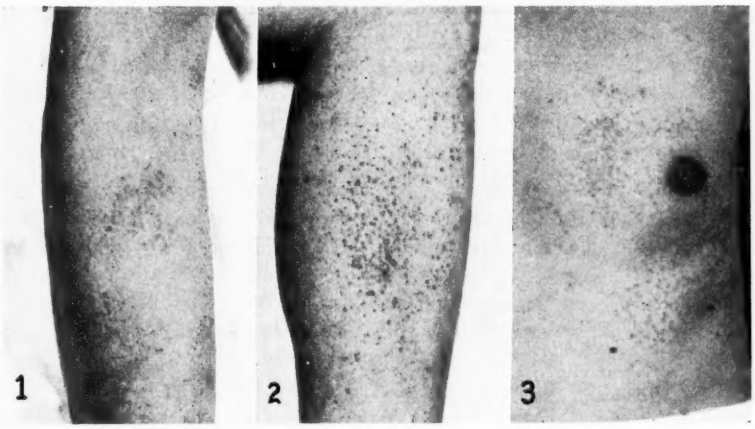

Fig. 1. Erythematous patch on arm.
Fig. 2. Hemorrhagic patch on leg.
Fig. 3. Erythematous patch on chest.

COMMENT

The analysis of the history, namely, the typical appearance of a finely papular erythematous rash on two different occasions, localized at the sites of application of electrode jelly, strongly suggested hypersensitivity to one or more of the ingredients used in its manufacture. The result of the scratch tests shows unequivocally that the only ingredient incriminated was the gum tragacanth.

Although sensitivity to gum tragacanth has been known and described before,[1,2] I believe this is the first case of dermatitis caused by electrode jelly to be reported.

CONCLUSION

At present, all makes of electrode jelly contain gum tragacanth, and because of the rarity with which hypersensitivity to it occurs, it does not seem practical to advise any modification in its composition.

It may be advisable, however, to use a pad impregnated with saline solution, instead of the jelly, on such individuals.

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REFERENCES

1. Feinberg, S. M., and Schoenkerman, B.B.: Karaya and related gums as cause of atopy. Wisconsin M. J., 39:734, 1940.
2. Gelfand, H.: The allergenic properties of the vegetable gums. J. Allergy, 14:203, 1943.

PERSONAL EXPERIENCE WITH "ANTIHISTAMINICS"

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THE author has had mild "grass" hay fever for many years. Usually, this is controlled by a few preseasonal or coseasonal injections. This year, however, the pollen concentration was heavier than usual, and moderately severe hay fever was experienced. It was decided to use some of the newer antihistaminics. The following drugs and dosages were used:

Decapryn	25 mg.
Neohetramine	25 mg.
Pyribenzamine	25 mg.
Thenylene	50 mg.
Trimeton	25 mg.

Results.—All gave prompt and satisfactory relief. Within one-half hour after taking any of these drugs all symptoms of hay fever were gone. This relief lasted from six to eight hours. Usually, there were no more severe symptoms that day.

Palatability.—All of the drugs used had a bitter and unpleasant taste. The only exception was Thenylene, which is a coated tablet. It was not possible to swallow any of the tablets without getting some local taste. The following list is in order of decreasing palatability.

Thenylene
Trimeton
Pyribenzamine
Decapryn
Neohetramine

Both Neohetramine and Decapryn produced nausea and epigastric distress; Neohetramine was the worst. Pyribenzamine produced intestinal cramps and a mild diarrhea.

Side Effects.—All the drugs used produced drowsiness and diplopia. The feeling was not unlike that of overindulgence in alcohol. It was difficult to focus the eyes, there was a feeling of lassitude, and thought was slowed. Under these circumstances, it was very difficult to carry on a medical practice. These symptoms lasted for four or five hours and were succeeded by a mild headache. They could be made to recede more rapidly, but not to disappear, by taking dexedrine sulfate 5 mg. In general the side effects were fully as distressing and more incapacitating than the hay fever.

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When one compares the side effects of the antihistaminics with those of ephedrine, there is much to be said in favor of this almost neglected drug. The chief side effect of ephedrine is stimulation; this is not necessarily bad. Many hay-fever patients are already depressed and fatigued—yet they cannot stop work. To give them a drug which may depress them still further is not fair. What most of them want is relief so that they can still carry on. Ephedrine is certainly indicated here.

SUMMARY

It is not often (perhaps not often enough) that doctors must take their own medicine. It is realized that one case does not mean much—except to the individual concerned. However, in this case, since the patient is also the doctor, he has drawn certain conclusions, namely:

1. The newer antihistaminics are often unpalatable and they may produce distressing side effects.

2. Ephedrine is not unpalatable and its side effects are no more unpleasant than those of the other drugs.

3. Perhaps an ephedrine combination for daytime use and one of the antihistaminics for bedtime would be the most sensible procedure.

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NETHAPHYL IN BRONCHIAL ASTHMA

(Continued from Page 663)

2. Nethaphyl gave relief in asthma without side reactions of tachycardia, palpitation, rise in blood pressure and nervousness.

3. No toxic reactions were severe enough to cause cessation of treatment with the drug.

4. Nethaphyl is a valuable addition to the armamentarium of oral sympathomimetic drugs.

BIBLIOGRAPHY

1. Becker, T. J., Warren, M. R., Marsh, D. G., Thompson, C. R., and Shelton, R. S.: Pharmacological and toxicological studies on 1-N-Ethylephedrine hydrochloride. J. Pharm. & Exper. Therap., 75:289, 1942.
2. Hansel, French K.: Nethaphyl in the treatment of nasal allergy and bronchial asthma. Ann. Allergy, 5:397, 1947.
3. Loveless, Mary H.: Therapeutic and side effects of Pyribenzamine and Benadryl. Am. J. Med., 3:296, 1947.
4. Snyder, Fred H., Goetze, Hartmann, and Oberst, Fred W.: Metabolic studies on derivatives of Beta-Phenylethylamine. J. Pharm. & Exper. Therap., 86:145, 1946.
5. Thompson, C. R., and Warren, M. R.: Acute and chronic toxicity studies on Theophyllin Aminoisobutanol and Theophyllin Ethylenediamine. J. Lab. & Clin. Med., 31:850, and 31:1337, 1946.

SOME UNCOMMON REACTIONS TO COMMON FOODS

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THE following case reports illustrate some uncommon reactions to common foods.

CASE REPORTS

Case 1.—In August, 1935, a six-year-old boy who had recently developed asthma according to the history given by the mother was first seen at the Guthrie Clinic. From early infancy this boy had had eczema. Hay fever of a seasonal type became manifest at the age of three. The mother strongly suspected foods as the cause of the asthma, because buckwheat, spinach and egg white caused hives very promptly after ingestion. It was further added that during the preceding two weeks, wheat products, oranges and bananas had been eliminated with apparent relief. Carrot or foods containing carrot, on coming in contact with the oral mucus membrane, would provoke an immediate severe angioneurotic edema. What was not appreciated about this child's sensitivity was learned within the next hour when a nurse failed to note a request that carrot be omitted from the group of foods for which tests had been requested. Within a minute after the patient had received an intradermal test to a commercial extract of carrot in 1:10 dilution, he went into profound anaphylactic shock. During the next several minutes it appeared that a fatal reaction to a skin test might be encountered. The mother and maternal grandmother seemed unperturbed by the incident. Within an hour the reaction subsided by the usual methods of treatment, except for an intense generalized urticaria which persisted for six hours. When the relatives were commended for their calm behavior, the mother replied, "We have seen him this bad many times before from eating carrot."

Case 2.—In August, 1936, a sixteen-year-old girl with seasonal hay fever presented herself for study and treatment. During the taking of a detailed history, the patient told of the most annoying reaction to the odor of fish. It made no difference whether the fish was canned or fresh. The odor of fish cooking was also intolerable. The reaction consisted of marked coryzal symptoms with sneezing, which was followed by severe angioneurotic edema of the face and mild asthma. The patient could incriminate canned salmon and tuna and such fresh fish as cod, mackerel, shad and halibut. She had no knowledge of what shellfish might do. Skin testing by the intradermal method gave insignificant reactions to eighteen of the common fresh and salt-water fish, including the shellfish. This patient has been followed for the past eleven years, and she still reacts, but less violently, to the substances named above. She has since married and has two children, both of whom have had atopic eczema due to the citrus fruits and wheat.

Case 3.—In September, 1943, a twenty-eight-year-old married woman was referred because she had had four convulsions since 1940, characterized by an aura which was followed by loss of consciousness and tonic and clonic convulsions, but no loss of sphincter control. The aura consisted of a loud buzzing sound in the right ear of a few seconds' duration before loss of consciousness and convulsions manifested themselves.

There were frequent "spells" of a characteristic petit mal type experienced by

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this patient several times each week. The patient was referred to us for neurological study. It was during the course of history-taking that the patient mentioned her fondness for orange juice and that only recently she had some misgivings regarding its tolerance. There was no family history of allergy. Skin testing by the intradermal method gave a slight positive reaction to chocolate and orange. Both foods were withdrawn from her diet for several weeks, during which time there were neither petit nor grand mal seizures. When the patient tried orange juice, she suffered several petit mal attacks within a few hours after ingesting the juice of a single orange. Chocolate was found to be the cause of no trouble. She has avoided oranges for the past four years and has been entirely relieved of her attacks.

Case 4.—A forty-three-year-old man who had suffered from severe migraine since the age of sixteen, and who knew that lamb, chocolate, celery, pork and fish, except the shellfish, would cause the attacks, presented a history of petit mal since the age of thirty-five. On a few occasions these had been severe enough to be embarrassing. The attacks always occurred with the onset of a migraine headache. By elimination it was found that chocolate and celery were the offenders.

The family history was interesting. His paternal grandfather had migraine and intestinal manifestations (diarrhea) from egg regardless of how it was prepared. The father of the patient suffered occasional but severe attacks of migraine from unknown causes, though it was felt that nervous and physical fatigue were the contributing factors. About age forty-eight the father ceased having migraine and began to have attacks of unconsciousness of short duration, preceded by an aura described as a pressure sensation in the head. There were no convulsive movements.

The mother of the patient was extremely allergic to acetylsalicylic acid, suffering angioneurotic edema. A sister of the patient is similarly affected on taking this drug. Two children of the patient are allergic. A son has seasonal hay fever and eczema, due to chocolate and all the citrus fruits. A daughter has eczema due to wheat, egg, banana, corn, apple and the citrus fruits.

The patient stated that the odor of lamb cooking provoked an annoying sense of nervous tension and excitability. The eating of lamb was followed within twelve hours by severe migraine. English walnut will provoke a restless night accompanied by unpleasant dreams, all of which are associated with the feeling that he is chewing tobacco, and are accompanied by a sense of nausea and profound salivation. The patient's wife has to awaken him because of the marked restlessness displayed in these attacks. The pillow is generously saturated with saliva in these attacks.

Skin tests by both the scratch and intradermal methods to foods and inhalants are negative. By trial diet, chocolate and celery have been found to be the causes of the petit mal attacks.

Case 5.—A twenty-three-year-old woman sought advice regarding desensitization to chocolate. Total abstinence was recommended since she suffered from severe asthma following its ingestion. She remonstrated because she loved the taste of chocolate, and its odor provoked a craving that was difficult to satisfy. To this she added an interesting comment which was readily confirmed by obtaining her old hospital records. She was born in 1915 in the obstetrical section of the Packer Hospital. During the first few days of life she presented a terrifying picture of severe respiratory difficulty which was reluctantly termed asthma. Her problem aroused considerable interest, and one of the many consultants who saw her thought that the mother's breast milk might be the cause and advised formula feedings. The response was favorable and dramatic, but the real answer to the problem was not forthcoming for some years. Not until the child became old enough to be given candy, and her marked sensitivity to chocolate was discovered, was the story com-

pleted. It was revealed that the mother was so strongly desirous of nursing this child that to insure a good supply of breast milk she indulged heavily in chocolate both prepartum and postpartum. Unquestionably, the mother's breast milk contained sufficient allergen to excite the response noted.

In order to accommodate this young lady, oral desensitization to chocolate, according to the suggestion of Kesten,[5] was tried. The result was not satisfactory, because even insignificant amounts of chocolate still provoked asthma within fifteen to thirty minutes, lasting for a day or more and requiring epinephrine at intervals for comfort.

DISCUSSION

A search of the literature will reward one with reports of unusual reactions or expressions of sensitivity to foods. Feinberg,[2] Rowe[6] Urbach[8] have covered these references in their textbooks. The first case presented in this paper represents a most intense reaction to a common food. It has been learned that the patient has improved encouragingly over the years although carrot still provokes an intense reaction, as does buckwheat, but other foods are tolerated without reaction.

The problem of epilepsy has intrigued many investigators. The above authors have considered the numerous available publications dealing with the probable allergic basis of this disease. In this writer's experience the two cases here reported are the only definite proven instances in a small but substantial series investigated. Two other cases of epilepsy might be added to this report, but they have not been followed for a sufficient length of time to justify their inclusion. It is not felt that idiopathic epilepsy is of allergic origin, but rather that epileptiform seizures can occur in individuals who are allergic and that food allergy is a contributory factor.

The case of sensitivity to chocolate occurring in the mother's breast milk may not warrant too much discussion because breast feeding seems to be unpopular. Shannon[7] and also Donnally[1] have shown, however, that food proteins can be excreted in breast milk in sufficient amounts to cause reaction in the nursing child. It is not surprising, therefore, that this patient should have had, in the first days of life, such intense reaction.

Finally, proof is not wanting of the fact that food odors, especially from food cooking, produce sufficient allergen in the air to cause reactions in susceptible individuals. Feinberg,[3] Hoersh,[4] and also Urbach[9] have presented their experiences and observations in this group of patients.

REFERENCES

1. Donnally, H. H.: The question of elimination of foreign protein in woman's milk. J. Immunol., 19:15, 1930.
2. Feinberg, S.: Allergy in Practice. Chicago: Year Book Publishers, 1944.
3. Feinberg, S. M., and Aries, P. L.: Asthma from food odors. J.A.M.A., 98:2280, 1932.
4. Horesh, A. J.: Allergy to food odors. J. Allergy, 14:335, 1943.
5. Kesten, Waters and Hopkins: J. Allergy, 6:431, 1935.
6. Rowe, A. H.: Clinical Allergy. Philadelphia: Lea and Febiger, 1937.
7. Shannon, W. R.: Anaphylaxis to food proteins in breast-fed infants. Minnesota Med., 5:137, 1922.
8. Urbach, E., and Gottlieb, P. M.: Allergy. New York: Grune and Stratton, 1946.
9. Urbach, E. J.: J. Allergy, 13:387, 1942.

THE SIGNIFICANT ALLERGENIC AIR-BORNE NONPATHOGENIC BACTERIA, THEIR INCIDENCE, TYPES OF ALLERGIES AND TREATMENT

A Three-Year Study

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IN the autumn of 1944, while summarizing the beneficial effects of the treatment of intrinsic allergies with an antibiotic,[1] we noticed that several of our patients, with definitely intrinsic allergies, who were cleared with antibiotic treatment, showed a recurrence of symptoms with the start of the autumn season. Their trouble was definitely of atmospheric origin, but as usual at this time of the year there were no pollens and only a few fungus spores found on our daily exposed slides. We then exposed petri dishes containing dextrose-agar daily to the open air. These exposures were made for five minutes on the seventh floor of an office building in the center of town. The exposed petri dishes were placed in the incubator and bacterial colonies developed in great numbers. This investigation began on October 10, 1944, and was continued until May 17, 1945. The organisms found on the test plates were always about the same, independent of atmospheric conditions, and also independent of the location, whether in town or in the suburbs. Regardless of the elevation above the ground, of the temperature of the outside air and the humidity, the colonies examined and identified by Dr. Borg of the Department of Microbiology of the University of Washington consisted of a great array of organisms characteristic for air-borne bacteria. Some were Gram-positive, like micrococcus tetragenus, micrococcus luteus, or Bacillus petasites; and some were Gram-negative like Pseudomonas aeruginosa, or spore-bearing bacteria like Bacillus megatherium, Bacillus mycoides, and Bacillus subtilis. Prominent in this group was Aerobacter aerogenes.

All these bacteria are nonpathogenic under normal conditions, but they are definitely allergenic and often cause allergic symptoms when the usual atmospheric allergens, such as pollens, mold spores, and various dusts, are not in the picture at all. Recognition of these not uncommon causes of allergic disorders is necessary in order to diagnose and treat some of the allergic diseases with which we have to deal.

In 1942 the American Association for the Advancement of Science published a volume entitled "Aerobiology" containing a number of articles about air-borne bacteria. In one of the articles Dr. E. C. Stakman says, "Relatively little is known about air-borne bacteria as possible allergens. The number of bacteria in the soil, their ability to survive in dry soil and their dissemination with dust suggest their possible effect on human beings and should be investigated."

Our investigation shows that a number of patients with intrinsic

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allergies caused chiefly by an allergy to air-borne (nonpathogenic) bacteria. Some of these patients will also react to pollens, mold spores and respiratory bacteria, but the important cause of their allergic troubles are nonpathogenic air-borne bacteria which are very common and widely distributed.

The progress in the diagnosis and treatment of allergies is made by gradual elimination of all the hitherto unknown causes of allergic disorders and their successful treatment. Of the many atmospheric causes of allergy, air-borne bacteria have been overlooked but should be investigated in every case where pollen, mold, and dusts have been found and treated and where there still remains a seemingly mysterious air-borne cause of allergies.

During this investigation between October, 1944, and the end of 1946, 423 colonies were studied and identified. A summary of the findings shows that they contained amongst others Bacillus mesentericus, Pseudomonas aeruginosa, Staphylococcus epidermidis and Micrococcus luteus. Others were identified as Micrococcus conglomeratus, Micrococcus candidus, Micrococcus epidermidis and Micrococcus flavescens. Further identifications revealed the presence of Micrococcus flavus, Micrococcus roseus, Bacillus cereus, Bacillus mesentericus, Bacillus petasites, Bacillus mycoides, Bacillus polymyxa variety acetoaethylicum, Bacillus aterrimus, Bacillus megatherium, and Bacillus vulgatus. All these bacteria are nonpathogenic under normal conditions, but they are definitely allergenic and often cause allergic symptoms when the usual atmospheric allergens, such as pollens, mold spores and various dusts, are not in the atmosphere.

TABLE I. SUMMARY

Total Number of Cases—155

Results of Treatment:			
Asymptomatic	29		
Marked Improvement	57		
Moderate Improvement	45	131	Positive Results or 84.4%
Slight Improvement	9		
No Improvement	11		
Moderately Worse	1		
Variable	2		
Condition Not Known	1		
	155		

Types of Allergies			
Rhinitis (Hay Fever)	60	Asthma	112
Urticaria	8	Dermatoses	23
Migraine	14	Gastrointestinal	3
		Mixed	62

CASE HISTORIES

Skin testing was done with a dilution of 1:1,000 of the stock vaccine. This dilution therefore contained four million organisms to the cubic centimeter. The skin reactions were usually very definite.

Case 1.—A married woman, fifty-two years of age, developed a severe cold in May, 1943. A persistent cough remained, and asthma was diagnosed by a physician in July, 1943. A definite respiratory wheeze was noticed after January, 1944. On the basis of skin tests a diagnosis of tuberculosis was made. The chest x-ray was nega-

tive. A positive sputum was reported in February, 1944. Treatment consisted of bed rest, epinephrine inhalations and various cough remedies. There was no improvement.

In March, 1944, the patient complained of a severe cough, purulent sputum, moderate dyspnea and wheezing. There was a mild atopic dermatitis on the lower extremities. Her clinical history revealed exacerbations of her symptoms on the seashore, out of doors, during the cool damp months, and on exertion. Physical examination revealed a typical moderately severe bronchial asthma and a dry, red, scaly, sharply demarcated macular rash on the lower extremities. Chest x-ray, blood count, and sedimentation rate were normal; PPD, 3-plus. Sputum: no acid-fast bacilli were found.

Family history was negative for allergies.

Skin tests: Intradermal tests for molds and the local pollens were positive. Intradermal tests were made for a mixture of Gram-positive and Gram-negative air-borne bacteria.

Treatment: Treatment with the reacting allergens, namely, mold and pollen extracts, and air-borne vaccines was started on April 13, 1944. Tests for airobacter aerogenes were done on May 10, 1944, and gave a 2-plus reaction.

In June, 1944, she began to improve and showed marked improvement after February 7, 1945. When last seen on November 4, 1946, she had only a slight cough and no asthma. The skin was clear, and she showed a marked gain in weight.

Case 2.—A woman, aged thirty-four, reported at this office February 2, 1944, complaining of recurring hives between January and August, and a mild cough. The symptoms started two weeks after moving to Seattle from Utah, four years previously. She thought that her symptoms seemed to be worse after eating pork, green beans, wheat, pineapple, chocolate, and walnuts. There was a definite aggravation during the spring and summer, from house dust and while riding out of doors.

A sister had hives.

Previous treatment consisted of injections taken three years previously after a series of skin tests. There was no improvement.

Physical and laboratory examinations were negative.

Skin tests were positive to summer and fall pollens, dust, respiratory bacteria, and a few foods.

Treatment consisted of hyposensitization to the inhalants and an elimination diet. Improvement was irregular and temporary.

Intradermal tests for air-borne bacteria were made on October 23, 1944, and treatment started immediately. There was noticeable improvement after April 4, 1945, with fewer and milder relapses. When seen on March 5, 1946, she had no respiratory symptoms and only occasionally a few hives.

Case 3.—A woman, twenty-nine years of age, gave a history of hay fever and asthma of eight months' duration. She had previously suffered from asthma from the ages of eighteen months to eight years. There are multiple family allergies.

Physical examination showed a well-nourished woman with the typical findings of allergic rhinitis and bronchial asthma. There was a nonpathological mitral systolic murmur.

The allergic study showed her to be sensitive to various pollens of trees, ferns, molds and respiratory bacteria. She was given hyposensitization treatment and was relieved until September, 1944, when she had a recurrence of her symptoms. She was tested intradermally with a 1:100 dilution of air-borne bacteria. She reacted moderately to Gram-positive bacteria. Proper vaccine was added to her treatment on October 25, 1944. Improvement was noticed immediately, and on March 3, 1947, she was discharged as asymptomatic.

Case 4.—A man, aged thirty-four years, an aeronautical engineer, stated on March 16, 1944, that he had had a substernal wheezing and a postnasal drip for three years following an attack of influenza. Exacerbations seemingly were not seasonal but were more frequent in damp, windy weather.

Previous injections containing a vaccine and house dust had given moderate temporary improvement. A subsequent series of injections produced no benefit.

There were no known allergies among his blood relations.

His past history was essentially negative.

Physical and laboratory examinations suggested no active pathologic condition.

Skin tests showed him to be allergic to dust, and coniferous tree pollen, and to a lesser extent, the spring and summer pollens.

He was tested for air-borne bacteria on October 27, 1944, and reacted positively to Gram-positive and to Gram-negative mixtures. Treatment with vaccines of both types of bacteria were started immediately, and improvement was noticed in January, 1945.

Temporary relief was obtained from hyposensitization treatment to the positive reacting allergens.

A subsequent left supraclavicular adenitis, edema and ptosis of the left eye, weight loss of 20 pounds, various gastrointestinal disturbances, and nervousness developed. He then remarked that he had had a mole removed. A diagnosis of metastatic sarcoma was made.

The patient moved to the Middle West, and the outcome of the case is not known.

Case 5.—On September 13, 1944, a woman, aged forty-eight years, complained of a chronic rhinitis of progressing severity of seven years' duration. It was nonseasonal. She noticed that the symptoms were much worse when she was exposed to house dust and temperature changes, and when constipated. There was occasional itching of the ears, nose and palate, and moderate aching in the right occipital area.

There was a past history of arthritis, angioneurotic edema in 1941, cholecytectomy 1938, and two tonsillectomies.

Family history for allergies was negative.

Previous treatment consisted of epinephrine injections and benzedrine inhalations which gave only slight relief. There had been no previous allergy study.

Physical examination was essentially negative except for an allergic-appearing nasal and pharyngeal mucus membrane.

Skin tests were positive for respiratory bacteria, late summer pollen, house dust, and a few foods.

Treatment consisted of an elimination diet, hyposensitization, and various symptomatic measures. There was no tangible improvement.

She was tested for air-borne bacteria on November 6, 8, and 15, 1944. Treatment began immediately with a Gram-negative mixture, and since then there has been a gradual, moderate improvement in her chief complaint, i.e., the rhinitis, although there have been episodes of various cerebral, gastrointestinal, and joint symptoms. She states that generally her condition is much better, and we feel that the prognosis is good.

Case 6.—A girl, age six, complained on January 14, 1944, of a chronic, perennial rhinitis since infancy. Exacerbations occurred during the summer and when indoors. There were no food dislikes and no history of food disagreements.

Many of her blood relatives present allergic complaints.

Physical examination was essentially negative.

Intradermal allergen tests were positive to spring, summer and fall pollens, and a dust mixture. On November 2, 1944, she was tested for air-borne bacteria and reacted strongly, more so to the Gram-positive mixture. Treatment was started, and

improvement began immediately. By May, 1945, the child was fine. She was free of symptoms, and treatments were stopped in September, 1945.

Case 7.—A woman, forty-two years of age, came to the office June 7, 1944, complaining of progressively severe asthma following a cold in January, 1943. She had had frequent colds for the preceding three years. The eating of peas had always produced nausea. The symptoms were aggravated when at home.

The past history revealed ringworm at age nine, and the removal of nasal polyps in 1934. She had spent her entire life on the West Coast.

There was no family history of allergy.

Physical examination elicited a slight roughening of the breath sounds, and a typically allergic-appearing nose and throat with small polyps in the right posterior nasal cavity.

The skin reacted violently to tests of summer and fall pollens, dust, fungi, dog hair, house dust, and respiratory bacteria. Local and general reactions occurred after the tests, requiring the administration of aminophyllin by vein. She was tested for air-borne bacteria on November 3, 1944, and reacted strongly to the Gram-positive mixture. On November 25, 1944, she was tested for another Gram-positive mixture, to which she reacted positively (2-plus).

Hyposensitization treatment produced a gradual and variable improvement. On one occasion an Arthus phenomenon from a dust injection occurred after the patient had unwittingly exposed herself to a massive dose of dust. The subsequent dilution of the dust extract had to be reduced from 1:1,000 to 1:500,000.

The air-borne vaccine was started November 3, 1944. Improvement was experienced about three weeks later. When last seen on January 20, 1947, she was symptom-free.

Case 8.—A man, aged sixty-two, with no family history of allergies, complained on March 20, 1944, of a severe morning cough accompanied by a marked dyspnea. The duration had been three years. Athletes foot had been present for many years, and he had had gout in the left great toe for one year. No specific previous treatment had been given.

Physical examination revealed a moderate postnasal drip, edema and hyperemia of the nasal and pharyngeal mucus membranes, a slight deviation of the nasal septum to the left, and an epidermophytosis on the left foot. Fluoroscopic examination of the chest showed a slight increased density in both apices, and a moderate myocardial hypertrophy.

The skin reacted to tests of tree and weed pollen, house dust and trichophytin. He was tested for air-borne bacteria on December 26, 1944, and gave mild reactions to Gram-positive and Gram-negative bacteria and to aerobacter. Treatment was started immediately, and improvement was noticeable.

Thereafter, improvement in symptoms was evident and on June 26, 1945, he was discharged as asymptomatic.

Case 9.—A man, fifty-eight years of age, reported April 3, 1944, complaining of asthma for one year, with the onset after he moved to the coast from Idaho. He had had a cough for four or five years. The initial trouble started after an attack of influenza. No known allergies existed among his blood relations. Past history was irrelevant.

Physical findings were not important.

All skin tests were negative except to the respiratory bacteria and fungi. Later tests showed him also sensitive to air-borne bacteria.

Hyposensitization treatment produced a marked but variable improvement.

The addition of the air-borne bacteria-vaccine to the treatment improved the situation, but the case terminated in only slight improvement. The treatment definitely

was not given a fair chance. It is well known that time is required to establish adequate immunity to practically all of the allergenic bacteria, and that necessary time was not at our disposal.

Case 10.—A housewife, aged thirty, came to the office June 5, 1945, complaining of asthma and hay fever of five years' duration.

She had had chronic recurrent colds since childhood. The symptoms were perennial, intermittent; worse in late spring and summer and after the menses. House dust seemed to aggravate her troubles.

Her past history revealed eczema and hives and frequent colds in childhood.

Multiple allergies are present in the maternal side of her family.

No improvement was experienced from a previous elimination diet following skin tests.

Physical examination revealed an occasional faint, evanescent wheeze. The heart, blood count, sedimentation rate, and Wassermann test were negative.

Skin tests were positive to coniferous tree pollen and various dusts.

Variable improvement was noticed after an elimination diet and injections consisting of the positively reacting inhalants.

The nonpathogenic air-borne bacteria vaccine was started September 11, 1945, three months after beginning of treatment. Some consistent improvement was beginning to be noticed five months later, February 27, 1946.

Excepting an intervening pregnancy which caused some aggravation, the patient is free of symptoms.

COMMENTS

Skin tests and the positive results of treatment with a vaccine made from air-borne bacteria demonstrate that an allergy to these bacteria exists in many cases. While assays against cultures of air-borne bacteria showed that they were affected moderately by penicillin and more strongly by streptomycin, we have found that treatment with a vaccine prepared from air-borne bacteria was a reliable, if slow, remedy in such conditions. The vaccines have to be very weak, as apparently these bacterial extracts are very active and strong. Our stock vaccines contained four billion organisms per cubic centimeter, which is the strength of most commercial bacterial vaccines. Treatment was started with dilutions of 1:1,000 of the stock vaccine. The dosage was slowly increased, and invariably good desensitization resulted. After some experience we found that we needed only three stock vaccines for treatment of all these cases of allergy to air-borne bacteria, namely, one made from Gram-positive, one made from Gram-negative air-borne bacterial cultures, and one from the Aerobacter group cultures. Skin testing was done with the same vaccines, diluted 100 or 1,000 times.

When an allergy to air-borne bacteria exists, the routine treatment for the usual allergens falls short of complete relief. Therefore, allergies to air-borne bacteria must be considered an important cause of symptoms and should be an intrinsic part of the diagnosis and treatment.

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REFERENCE

1. Schonwald, Philipp, and Deppe, E. F.: Penicillium antibiotic in the treatment of intrinsic allergies. Northwest Med., 44:10, (Jan.) 1945.

ALLERGIC ECZEMATOUS CONTACT-TYPE DERMATITIS FROM ODD THINGS OR IN ODD WAYS

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THE following case reports illustrate situations in which well-known eczematogenous allergens caused dermatitides in unusual places or by uncommon mechanisms. In one case an unlikely contactant caused an eruption on skin sites on which more obvious substances seemed implicated.

Case 1.—Allergic eczematous contact-type dermatitis of the buttocks from the *wood* of a plastic-paint-covered and undamaged toilet seat.

C. M., a boy, aged twelve, presented an eczematous eruption on the lower quadrants of the buttocks and the upper portions of the thighs. The localization of the rash very plainly implicated a toilet seat. The eruption was more extensive on one side than the other due to the fact that the patient characteristically sat in such a position as to cause greater contact and exposure on the more affected side. Patch tests with slivers from the painted side of the toilet seat were negative, but strongly positive reactions (4-plus) was elicited by the unpainted wooden side. This unexpected finding was confirmed by repeated tests. The species of wood was not botanically identified.

Case 2.—Allergic eczematous contact-type dermatitis of the fingers, neck and lips from the dyes of nylon threads.

A. G., a seamstress, specialized in sewing button holes with nylon thread. An eczematous eruption appeared on the fingers, lips and across the neck in the fashion of a necklace. The patient herself suspected the nylon thread as the cause of her dermatosis and proved the point prior to medical investigation by tying a piece of the material around her wrist. Within two days a vesicular dermatitis in the shape of a bracelet promptly occurred. The lesions on the fingers corresponded to the way in which the nylon threads were manipulated in the sewing process; the eruption on the neck corresponded to the places where lengths of thread were held for successive use; the cheilitis was caused by wetting of the threads with the lips to facilitate threading of the needles.

This case, among others, was extensively studied by Dobkevitch and Baer.[1,2] These workers showed that in their cases the allergen involved in nylon-stocking dermatitis was the dye. They explained further that the sensitizing dyes which had been used in nylon stockings were converted on the skin into compounds which are chemically and immunologically related to paraphenylenediamine in its conversions.

Table I is an abridged protocol of the patch tests performed on this patient.

Case 3.—Allergic eczematous contact-type dermatitis of the face and other parts of the body from contamination of innocent cosmetics with nail polish or other strong sensitizing agents.

B. W., a housewife, presented an eruption on the brow, cheeks, neck and hands. Clinical experience suggested a cosmetic applied widely to the body. Patch tests were performed as shown in Table II.

This case is representative of a group of patients who are very sensitive to nail

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TABLE I

Test Substance	Reading	Remarks	Dates
Waxed nylon thread, navy	1 plus		
Waxed nylon thread, brown	2-3 plus		
Waxed nylon thread, black	2-3 plus		
Wax, as is	Negative	Note positive reactions to paraphenylendiamine and to rubber glove in addition to the positive reactions to the various nylon threads.	Tested 11/9/47
Paraphenylendiamine (2% in pet.)	2-3 plus		
Unwaxed nylon thread, gray	1-2 plus		Read 11/11/47
Unwaxed nylon thread, tan	1-2 plus		
Unwaxed nylon thread, brown	1-2 plus		
Control gray silk thread	Negative		
Nickel sulphate, 5% aq. sol.	Negative		
Rubber glove, stock specimen	1-2 plus		
Brand A nylon hose	3-4 plus		Tested 11/29/47
Brand B nylon hose	3-4 plus	Note positive reactions to all brands of nylon hose including patient's, and to her rubber glove.	
Brand C nylon hose	3 plus		Read 12/1/47
Brand D nylon hose	1 plus		
Patient's nylon hose	2 plus		
Patient's rubber glove	3 plus		
Brand E dyes I-IV, as is	Negative		Tested 12/20/47
Brand E dyes V & VI, as is	2-3 plus	Note positive reactions to several dyes and absence of reaction to undyed nylon thread.	
Nylon thread, undyed	Negative		Read 12/22/47
Brand C dyes I & II, as is	3-4 plus		
Brand B dyes I & II, as is	3-4 plus		

TABLE II

Test Substance	Reading	Remarks	Dates
Cleansing cream	3 plus	Note strong reactions to cleansing cream and to nail polish.	Tested 3/26/47
Orange skin cream	Negative		
Skin lotion	Negative		Read 3/28/47
Nail polish	2 plus		
Cleansing cream (material taken from bottom of jar)	Negative	Note absence of reaction to uncontaminated portion of cleansing cream.	Tested 4/2/47
			Read 4/4/47
Nail polish	2 plus		
Skin lotion	Negative	Note confirmation of previous test findings and proof of contamination of other preparations with nail polish.	Tested 4/7/47
Orange skin cream (material taken from top of jar)	1 plus		
Nail polish	3 plus		Read 4/9/47
Mum (deodorant)	Negative		
Cold cream (material taken from bottom of jar)	Negative		
Cold cream (material taken from top of jar)	2 plus		

polish and who, at first, give the impression of being sensitive to other cosmetics which are not related to nail polish. Such coincidence would not be remarkable if the reactions were due to concomitant sensitivity to nail polish and, say, hair lacquer, but concomitant sensitivity to nail polish and several creams must be statistically rare. Upon analysis it has been repeatedly discovered that polish from the finger nails easily contaminates other cosmetics concurrently applied.

In Tables III and IV, and in the following paragraph, are presented additional miscellaneous cases which reveal, by critical patch testing with selected portions of the implicated substances, allergenic contamination of innocent cosmetics by notorious sensitizing agents.

D. B., a worker in leather belts and handbags with an eruption of the hands, antecubital fossae and axillae, was discovered upon routine testing to be very strongly reactive to paraphenylendiamine and moderately so to the commercial deodorant she was currently using. Critical patch testing, however, showed the same strong re-

TABLE III. CASE OF C. S.

Test Substance	Reading	Remarks	Dates
Nail polish	3 plus	Note strong reaction to nail polish and suggestive reaction to cold cream.	Tested 6/2/47
Cold cream	Plus-minus		
Paraphenylendiamine (2% in pet.)	Negative		Read 6/4/47
Lipstick	Negative		
Face powder	Negative		
Pyrethrum, as is	Negative		
DDT (5% in acetone)	Negative		
Cold cream (material taken from top of jar)	2 plus	Note proof of contamination of cold cream by unequal reactions corresponding to degree of contamination.	Tested 6/4/47
Cold cream (material taken from bottom of jar)	Plus-minus		Read 6/6/47
Nail polish	3 plus		

TABLE IV. CASE OF M. M.

Test Substance	Reading	Remarks	Dates
Bath powder	Negative	Note apparent implication of sub-tint cream alone. Test with nail polish not yet done.	Tested 4/23/47
Mascara cream	Negative		
Rouge	Negative		Read 4/25/47
Sub-tint cream	2 plus		
Wave lotion	Negative		
Perfume	Negative		
Face powder	Negative		
Lipstick	Negative		
Nail polish	2 plus	Note proof of contamination of sub-tint cream by nail polish.	Tested 4/25/47
Sub-tint cream (old jar)	2 plus		
Sub-tint cream (new jar)	Negative		Read 4/27/47

actions to paraphenylendiamine, to samples of her tan, brown, blue, black garments, and to occupational materials, but a negative reaction to a newly purchased specimen of the same deodorant. In this instance the old jar of deodorant must have been contaminated by traces of the dye clinging to the fingers from domestic or occupational manipulations.

Case 4.—Allergic eczematous contact-type dermatitis of the female breasts from sponge rubber prostheses ("falsies," "gay deceivers").

T. G., a stenographer, acquired and wore a pair of sponge rubber mammary prostheses. About two weeks after use of these devices, an erythematous, scaly eruption appeared on the outer, lower quadrants of the true mammae. Patch tests with pieces of the sponge rubber on unaffected sites of the breasts reproduced the eruption in these areas.

COMMENT

The first case, describing the sensitivity to wood of a toilet seat heavily covered with paint, illustrates a phenomenon incredible to the inexperienced, namely, the ability of an allergen to pass through seemingly impervious barriers and successfully challenge the skin. However, the positive patch tests, and the clinical tests of improvement upon avoidance and exacerbation upon re-exposure, prove the causal relationship. Such instances lead to the inescapable conclusion that some allergens have remarkable capacities to elicit reactions with amounts that would appear to be chemically undetectable.

The second case report illustrates, among other things, the well-known importance of occupational operations in localizing the sites of contact-type dermatitis. More important, it further demonstrates that, for some substances, minor additions or unavoidable traces of agents that are of small compositional importance in the parent mass (azo-dyes in the case in point) may be responsible. Similar examples are to be found in the minute amounts of formalin in plastics and in soap which provoke and evoke allergic sensitivity, whereas the actual plastic or other soap ingredients may be inert. Most important of all, it reveals strikingly the phenomenon of cross-sensitization between allergens. This fact, as had been fully discussed and stressed by Sulzberger,[3] explains the persistence and chronicity of some allergic dermatoses in spite of apparent avoidance of causal substance. Appreciation of the situation will sharpen search for immunologically related agents and will inevitably lead to discovery and cure in a greater percentage of cases.

The third report illustrates the very common circumstance in which tests can be misleading if their interpretation is hasty or uncritical. A knowledge of the intimate habits of persons of both sexes and of all types and stations is shown to be of value. If one were to devise a means of tracing the transport of substances by the hands to other parts of the body, the locations on which deposit is made would surprise the unimaginative. Far-flung distribution of substances by handling, and the multiplicity of common substances that are of eczematogenic potential, are two very significant considerations in discovering causative agents and in solving obscure problems. In the cases cited, the contamination of innocent preparations by minute amounts of powerful sensitizers may either incriminate harmless agents without implicating the actual offenders, or, if the contaminating event is not realized, may perpetuate an eruption despite removal of the apparently offending substance.

The fourth report is representative of similar, more banal events like eruptions from hearing aids, telephones, and artificial limbs.

REFERENCES

1. Dobkevitch, S., and Baer, R. L.: Allergic eczematous dermatitis due to dyes in nylon stockings. J. Invest. Dermat., 8:419, (June) 1947.
2. Dobkevitch, S., and Baer, R. L.: Cutaneous cross-hypersensitivity to azo-dyes in nylon stocks and to paraphenylendiamine. J. Invest. Dermat., 9:203, (Oct.) 1947.
3. Sulzberger, M. B.: Dermatologic Allergy. Springfield, Illinois: Charles C Thomas, 1940.

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A CLINICAL EVALUATION OF A NEW ANTIHISTAMINIC DRUG, "ANTISTINE"

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WITH the advent of the new antihistamine drugs, the field of palliative therapeusis in allergy has been greatly enhanced. In the last year or so there have been numerous reports on the use of Benadryl and Pyribenzamine. Here we have attempted to give a clinical analysis of the efficiency of one of the newer antihistaminics, namely, Antistine.*

Antistine is Ciba's trade name for an antihistaminic preparation, whose chemical formula is phenyl-benzylamino methyl-imidazoline. For oral medication, the hydrochloride salt is used, while topically in the eye and nose the sulfate is preferred. Animal experiments[3] would seem to indicate that this drug is from two to ten times less toxic than Pyribenzamine, depending on the route of administration. From evidence presented by animal experimentation[3] it would seem that Antistine has definite antihistamine activity.

Several European reports have been published on the use of this drug. Schindler[7] investigated its effect on thirty-nine allergic patients. Of this number, ten had bronchial asthma, eleven had urticaria, fifteen had pruritic conditions. He used the oral, subcutaneous and intravenous routes of administration. His average daily dose was 300 mg. orally; however, twice this amount was tolerated. Parenterally, the dose varied up to 300 mg. No unpleasant secondary effects were observed. He found that the therapeutic effect in urticaria was very good; in pruritus and in some cases of asthma, it was good. In two cases of erythema nodosum it was ineffectual; however, the articular pains in a case of scarlet fever rheumatoid disappeared on the second day of treatment.

Brack[2] found that Antistine, in addition to its inhibiting effect on itching produced by histamine, had a slight local anesthetic effect. He found that, in proper dosage, it will reduce or counteract the itching in urticaria, eczema, neurodermatitis, prurigo, lichen ruber planus, psoriasis, and nervous pruritus without skin changes and in scabies. To completely suppress the itching, doses which caused temporary mild dizziness were occasionally employed. In urticaria, not only the itching but the skin changes were prevented. Direct influence on the skin changes in other dermatologic conditions was not observed. The only undesirable secondary effect observed was occasional mild dizziness.

Bourquin[1] used Antistine eye drops in numerous eye conditions, and recommends it especially in allergic eye conditions. He found that photophobia, itching and lacrimation were favorably affected. Meier and

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*Antistine was supplied through the courtesy of the Ciba Pharmaceutical Company, Summit, N. J.

Bucher[5] in animal experiments found that Antistine has definite antagonism to histamine when applied locally or generally. They[6] further demonstrated that this drug does not inhibit the antibody production stimulated by repeated antigen injections; in fact, animals given Antistine had a considerably higher titre, and they postulate that this might have been due to the fact that these animals were able to tolerate a much larger amount of antigen which might possibly have been the basis for the increased antibody production.

Friedlaender and Friedlaender[4] found that Antistine afforded guinea pigs protection against histamine shock. They further found that in 50 to 100 mg. doses it gave symptomatic relief in the majority of cases of allergic rhinitis and urticaria. Less benefit was apparent in asthma, atopic dermatitis, contact eczema and allergic headache. They felt that Pyribenzamine was more effective when used in the same patient, although a small percentage found Antistine superior. Antistine eye drops produced symptomatic relief of burning and itching in cases of allergic conjunctivitis. The side effects from Antistine were generally less frequent than with Pyribenzamine, and in a group of patients in whom the two drugs were compared, it was found that frequently those unable to tolerate Pyribenzamine were able to tolerate Antistine in effective dosage.

In our series of cases, there was no attempt made at selection of patients. The drug was given for the presenting symptoms in cases of asthma, hay fever, atopic eczema, contact type eczema, allergic conjunctivitis, and gastrointestinal allergy. Many of these patients were undergoing hyposensitization therapy, and for one reason or another, were symptomatic. Of these patients, many were just starting therapy for the first time, while others who had been under treatment for ragweed hay fever for a number of years, developed either tree or grass hay fever for the first time this year, necessitating some palliative therapy.

Of the patients taking the drug the duration varied from one week to 133 days. The dosage employed by these patients was a 100 mg. tablet three to four times daily. Many of the patients had never been on any previous antihistamine therapy while the others had been on Benadryl or Pyribenzamine and, because of the severity or persistence of side effects, had had to discontinue them. One patient was hospitalized on two occasions last year, due to severity of side effects from Benadryl and Pyribenzamine. He was able to tolerate 300 to 400 milligrams of Antistine with the only side effect being slight nausea.

Table I shows the clinical results obtained with the use of Antistine. The various categories into which these patients fitted are shown; in addition, the patients are divided into adults and children. Although the results with asthmatic symptoms were disappointing, the cough was controlled in most cases. In the four cases of conjunctivitis, only local therapy consisting of 0.5 per cent Antistine eye drops was used.

We found the drug to be very efficacious in children because adequate

TABLE I. CLINICAL RESULTS WITH ANTISTINE

Allergic Manifestation	Adult	Children	Fair		Good		Excellent		Poor	
			No.	%	No.	%	No.	%	No.	%
Hay Fever	24	15	6	15	20	51	10	26	3	8
Perennial Allergic Rhinitis	12	7	6	32	5	26	3	16	5	26
Asthma and Hay Fever	14	10	3	12	14	58	2	8	5	21
Chronic Urticaria	4	0	0	0	1	25	0	0	3	75
Atopic Eczema	3	1	0	0	1	25	1	25	2	50
Contact Eczema	3	0	0	0	2	66	0	0	1	33
Conjunctivitis	3	1	0	0	2	50	2	50	0	0
Gastro-Intestinal Allergy	1	1	0	0	0	0	1	50	1	50

These cases were evaluated both subjectively and objectively within the limits of such an evaluation, which, it must be admitted, is frequently not good. Subjectively we depended on the patient's statement as to how he felt. Objectively we examined the patient. Those cataloged as poor had no relief whatsoever. Those classified as fair had equivocal results; those reported as good had approximately 50 per cent relief, and those who were listed as excellent had either complete or practically complete relief.

TABLE II. SIDE EFFECTS* OBSERVED WITH ANTISTINE

Nausea	6
Sneezing (?)	1
Dryness of mouth	4
Dizziness	2

*In one case the severity necessitated discontinuance of the drug.

TABLE III. COMPARATIVE SIDE EFFECTS IN PATIENTS WHO HAD TAKEN PYRIBENZAMINE AND/OR BENADRYL AND/OR ANTISTINE.

	Number of Patients	Number having Side effects	Per Cent
Antistine	99	13	13†
Pyribenzamine	21	10	47*
Benadryl	18	16	88**

*Of these, five patients had to discontinue because of severity of side effects.
**Of these, sixteen patients had to discontinue because of severity of side effects.
†One couldn't take Antistine.

dosage could be given while side effects were minimal. It is interesting to note that of the few side effects that our patients experienced, none occurred in children.

From our experience, we feel that the 100 mg. Antistine tablet has roughly the therapeutic effect of the 50 mg. Pyribenzamine tablet with, however, less side effects. When this study was first undertaken, the tablets were in 50 mg. size, and with this amount, no side effects were observed, but therapeutic results were also quite negligible. We then tried 100 mg. on a number of patients, and palliative effectiveness increased. Subsequently, after discussion with Dr. Mayer of Ciba, the tablets supplied to us were 100 mg. size.

In Table II we have tabulated the few side reactions which our patients experienced. In one of these, the symptoms were severe enough to necessitate discontinuance of the drug. This patient, strangely enough, experienced severe sneezing spells each time she took a tablet; this occurred on three successive days. She had a perennial allergic rhinitis, and at the time of medication her complaint was a stuffy nose, but she had no sneezing spells.

Table III shows the comparative effects in some patients who had taken either Pyribenzamine and Antistine, Benadryl and Antistine, or had taken

all three. The figures on Pyribenzamine and Benadryl are obviously misleading for several reasons: firstly, the number of patients on whom the comparison was made, was quite small. Secondly, and more important, these represent only those patients who had taken Pyribenzamine or Benadryl and, because of side effects or lack of therapeutic results, were put on Antistine. Many of our other patients, who were on Pyribenzamine or Benadryl for short periods of time, experienced no side effects and had good palliative therapeutic results; they were not included in this study.

It might be well at this time to point out, as shown by Friedlaender and Friedlaender,[4] that although the antihistaminic activity of Antistine, as determined experimentally in the guinea pig, is considerably less than that of Pyribenzamine, we, as well as they, did not find such a discrepancy to be true insofar as clinical effectiveness in allergic conditions is concerned. This would appear to support the contention of many, that histamine plays only a partial role in allergic reactions.

SUMMARY

1. Antistine, the trade name for a new antihistaminic manufactured by Ciba, afforded symptomatic relief in a majority of hay fever patients to whom it was given. Such results were less evident, but still present, in many with perennial allergic rhinitis. In asthma, the results were disappointing except for the relief of coughing.

2. In only four cases of urticaria, the results were poor in three cases and good in one case. The drug showed some suggestive effectiveness in two patients with atopic eczema and two with contact eczema.

3. In four cases of allergic conjunctivitis, the results were uniformly good.

4. In two cases of gastrointestional allergy, one responded very well, and in the other case no effect was observed.

5. The drug was very efficacious in children, because adequate dosage could be given with minimal side effects.

6. It would appear, that 100 mg. of Antistine has roughly the therapeutic effect of 50 mg. Pyribenzamine, with, however, much less side effects.

REFERENCES

1. Bourquin, J. B.: A new synthetic antihistaminic substance (Antistine) and its use in ophthalmology. Schweiz. med. Wschnschr., 76:296-300, (April 6) 1947.
2. Brack, W.: Significance of synthetic antihistamines for dermatology. Schweiz. med. Wchnschr., 76:316, (April 13) 1946.
3. Ciba Research Laboratories Report. Sent to us by Ciba Pharmaceutical Co.
4. Friedlaender, A. S., and Friedlaender, S.: An evaluation of Antistine, a new antihistaminic substance. Paper presented before American College of Allergists, June, 1947. (To be published.)
5. Meier, R., and Bucher, K.: Pharmacology of 2-(N-phenyl-N-benzylaminomethyl) imidazoline (Antistine), A new synthetic antihistamine substance. Schweiz. med. Wchnschr., 76:294-296, (April 6) 1946.
6. Meier, R., and Bucher, K.: Influence of antihistaminic substance on antibody production, experimentia, 2:141, (April 15) 1946. (Sci. Labs. Ciba, Basle, Switz.)
7. Schindler, O.: Clinical investigations with antihistamine substance, Antistine. Schweiz. med. Wchnschr., 76:300, (April 6) 1946.

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Abstracts of lectures presented at the first scientific meeting, April 15, 1948

PROGRESS IN ALLERGIC RESEARCH WORK

Part I. Theoretical.

By E. RAJKA

A REVIEW of experiments for better definition of allergens, their chemical structure, was given, with special emphasis on the importance of the determining group of complex allergens, as well as the investigation of common group allergens. The limits of sensitization in related chemical substances were emphasized with notes on the pathogenesis of occupational diseases; experimental sensitization may be similar to, or related to, occupational eczema. Complex allergens may be formed in the organism itself.

The structure of reagins is dealt with in experiments (synthetic antibody); reagins seem to be serumglobulins, modified by the effect of chemical configuration and molecule groups of allergens.

The importance of lymphocytes has been emphasized. The most recent passive transfer tests with peritoneal exudates rich in lymphocytes, appearing in infective asthma and experimental eczema (Landsteiner, Chase, Haxthausen) point towards the action of lymphocytes in similar conditions. Kallós thought that the lymphocytes can be transformed into macrophage cells, and therefore belong to the group of macrophages. The problem of thermostable inhibitory substances is touched upon in relationship to the percursory Lehner-Rajka dereagin (Urbach).

Part II. Clinical

By K. HAJOS

It is emphasized that sensitization and the establishment of local allergic symptoms is possible in every organism, but such local allergic symptoms and experimental results do not coincide with changes in the origin of allergic diseases. Recent research work justifies the importance of heredity and the special reaction of the whole organism beside immunobiological reactions in the development of allergic diseases. This was called the allergic constitution, allergic diathesis, et cetera. Lately, allergic personality is the term which contains the A and VM groups (Mitchell). The two asthmatic groups prove that immuno-biology cannot explain altogether the origin of asthmatic cases, for if we speak of endogenous, or Mitchell's VM groups in the origin of asthma, we emphasize other factors in its pathogenesis, rather than immuno-biological reactions alone.

It seems to be difficult to diagnose the allergic pathomechanism of bronchial asthma in advanced age, also that of migraine and chronic rhinitis. Purely immuno-biological explanations of conditions lately considered of allergic origin seem to be not quite satisfactory.

Frustrations of World War II, such as changed life conditions, unsatisfactory nourishment, strain and stress, and severe psychic trauma, influenced the appearance of allergic diseases and paroxysms, as well as aggravated or abolished symptoms. Personal investigations seem to differ from those published in the American literature, where depletion, undernourishment, physical and psychic strain and stress of military service, in short—psychic causes, were thought to encourage the appearance of allergic symptoms. In our cases, war conditions, sieges, deportation, life in internment camps and the ghetto, undernourished, brutal and unfair persecution of large social groups established a special physical and psychic environment where constant fear and special conditions diminished the irritability of the central nervous system, the vegetative centers and endocrine functions, and thus abolished excitatory factors evoking allergic reactions. We found that in such severe physical and mental conditions asthmatic attacks, vasomotor rhinitis, urticaria, and giant edema had not been observed. The final cause may be diminished irritability of the hypothalamus and the cortex.

Satisfactory treatment of allergic paroxysms and of asthmatic attacks may be obtained by the aid of psychosomatic medical theory, where the special form of psychiatry is of less importance than effective influence on allergic manifestations.

BONE MARROW AND ANAPHYLAXIS

By G. FILIPP, A. BAN and L. MATKO

The blood count and myelograms of twenty-four anaphylactic cats were investigated. Ten cats had been sensitized with human serum, the anaphylactic shock being established by re-injection into the saphenous vein. The shock was more intense after rich protein diet. In the peripheral blood count, erythrocytes slightly increased thirty to sixty minutes after the re-injection, while the leukocytes dropped to 50 to 30 per cent of the original number. Leukopenia was followed by corresponding relative lymphocytosis.

First, an increase in eosinophil polymorphonuclear leukocytes, and later in eosinophil staff cells was noted. Two hours after re-injection, neutrophil staff cells increased with a decrease of the same in the marrow, while normoblasts appeared in the peripheral blood after shock. One hour after re-injection, the reaction of the leukopoiesis culminated in the expulsion of mature myeloid cells, and maturation-inhibitory reaction was established in the immature myeloid cells. The latter leads to an increase in immature myeloid cells, such as myelocytes and promyelocytes. There is a rise of lymphocytes associated with that of myelocytes. Increase of

lymphocytes in the marrow is but relative and the total number of myeloblasts does not change.

Metamyelocytes remained unchanged in four cases, they increased in number in three cases, and in three others a decrease was noted. Eosinophil leukocytes disappeared from the marrow during shock and increased on the peripheral circulation. There was a definite increase in lymphoid and plasmo-cellular reticulocytes of the myelopoietic apparatus at the summit of the reaction, which confirms uniform reaction of the marrow to allergens. Myelopoietic reaction lasts twenty-four hours. Twenty-four hours after re-injection, the peak of erythropoietic reaction is demonstrated by hyperplasia and respective peripheral erythrocytosis. At the height of myelopoiesis and erythropoiesis, we find the greatest number of erythrocyte and leukocyte divisions in the marrow.

By hematological investigations of cats which died in anaphylactic shock, we found leukocytosis and pan-myelophtisis. Inhibition of maturation of leukocytes is being considered as a milder form of pan-myelopathy compensated by the marrow. After the shock, we always found in the marrow myelocytes with so-called ring-nuclei, which compensated in our cases for the maturation-inhibitory effect. As the center of the myelocytic nucleus dissolved, the ring grew gradually thinner, later it broke up, and myelocytes matured to staff form without passing the metamyelocytic stage.

Ten cats were re-injected immediately into the marrow after sensitization. Peripheral changes were as follows: erythrocytes, neutrophil leukocytes, lymphocytes and staff cells did not change in number; eosinophil leukocytes disappeared from the peripheral blood. Changes in the marrow were: culmination of myelopoiesis in one hour; that of the erythropoietic reaction four hours after re-injection with very pronounced local eosinophilia with peripheral eosinophilopenia pointing towards migration to the marrow.

In four cases, agranulocytosis was established by means of allergic reactions. It is certain that the eosinophilia derives from the bone marrow.

DISCUSSIONS

L. Mosonyi: Years ago M. investigated differential blood count and myelogram in aspirin and barbiturate poisoning. He found the most prominent changes to be "shift to the left," mild leukocytosis, increase in number of immature cells in the marrow, all appearing by milder poisoning, while no change was seen in the beginning by other groups. In very mild cases, there had been no other changes, while in very severe cases the normal blood count was regained through the moderate severe cases. This may be explained by shock-effect, after which the reaction of the marrow can be established alone.

K. Hajos: Discussion of exact hematological experiments confirmed earlier investigations, showing that the eosinophilia observed in allergic-

anaphylactic reactions originated from the fact that eosinophil leukocytes are being formed in the bone marrow, and wander to the site of allergic and anaphylactic reactions. Local eosinophilia may be explained by substances formed during localized immuno-biological reactions. Earlier experiments proved that in the peripheral blood the number of eosinophil leukocytes showed a periodical change with increase before the attack, followed by peripheral decrease, as well as local accumulation and sometimes excretion.

INFLUENCE OF THE AUTONOMIC NERVOUS SYSTEM ON THE ESTABLISHMENT OF SERUM-SICKNESS

By L. LENGYEL

The state of the autonomic nervous system of forty-nine patients suffering from diphtheria, and inoculated for the first time, was studied after intravenous injection of 0.01 mg. of epinephrine.

1. All patients showing increased vagotonia had serum-sickness of longer duration with more severe clinical symptoms than in those whose autonomic nervous system was well balanced. Difference of the two groups was significant.

2. Incubation time showed no prominent difference between the two groups.

It was concluded that the state of the autonomic nervous system is an important disposing factor in the origin of serum-sickness. Its effect lies less in reagin formation than in its influence on the symptoms established by tissue cells during the allergin-reagin reaction.

3. Increased sympathetic tone diminishes susceptibility to diphtheria.

CRYMOTHERAPY AND ANAPHYLAXIS

(Continued from Page 668)

SUMMARY

Refrigeration in guinea pigs appears to slow the onset of anaphylactic symptoms. It prevented fatality, however, in only 38 per cent of the test animals, a figure not considered significant. It did not prevent the onset of signs of anaphylaxis in any of the animals. It seemed to delay the onset of signs of histamine shock, without preventing fatal shock.

REFERENCES

1. Fay, Temple: Observations on prolonged human refrigeration. New York State J. Med., 40:3, (Sept.) 1940.
2. Frank, D. E.: Use of crotalin in the prevention of anaphylactic shock in guinea pigs. Ann. Allergy, 5:156, 1947.
3. Frank, D. E.: The use of papaverine hydrochloride in the prevention of anaphylactic shock in guinea pigs. J. Immunol., 52:59, 1946.
4. Frank, D. E., and Harris, M. C.: Histaminase; experimental and clinical studies. M. Clin. North America, 25:849, 1941.
5. Whittemore, W. L.; Lisa, J. R., and Sauer, P. K.: Crymotherapy and its relation to hibernation. New York State J. Med., 40:21, (Nov. 1) 1940.

EVALUATION OF THERAPEUTIC SUBSTANCES EMPLOYED FOR THE RELIEF OF BRONCHOSPASM

II. Historical Development and Methods

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THE search for a common substance active in the protean manifestations of allergy and anaphylaxis in animals and man has involved many investigators and countless studies over the past four decades. In these varying and conflicting reports, two substances, histamine and acetylcholine, have often been considered possible chemical mediators of allergic phenomena. Both of these substances are capable of producing dyspnea and bronchospasm in asthmatic subjects and may be used in the evaluation of agents capable of protecting against these effects. With this technique a method of assay in humans of the relative value of new and of accepted therapeutic agents for the relief of bronchial asthma has been evolved. The development and present status of this technique is the subject of this report.

HISTAMINE

Histamine (beta-iminazolylethylamine) was recognized among the active amines of ergot by Barger and Dale in 1910.[5] In the same year, Ackermann[1] demonstrated that the normal bacterial flora of the intestinal tract produced large amounts of the same compound by the decarboxylation of histidine. Dale at once began investigations on the possible physiological role of this substance and concluded that "the immediate symptoms of poisoning by beta-iminazolylethylamine . . . are to a large extent those with which an animal responds to an injection of . . . normally inert protein to which it has been sensitized."[21]

Thus, within a year after histamine was first noted to be a pharmacologically active material, and long before it was demonstrated to be present in mammalian tissues (Best et al, 1927[8]), the striking similarity between the effects of administered histamine and the phenomena of anaphylaxis in animals was observed. However, Dale, together with most subsequent investigators, carefully refrained from assigning a causal role to histamine in this situation.

Much evidence bearing on the possibility that histamine formation or release is the basic mechanism in allergic and anaphylactic phenomena has been accumulated. The evidence for such a concept has been summarized by Dragstedt[33,34]: (1) As originally noted by Dale, the effects following the administration of histamine are similar to anaphylactic shock;[21] (2) histamine is present in mammalian tissues in concentrations quantitatively sufficient to explain the phenomena of anaphylaxis on the basis of released histamine;[78,62,35,36] (3) allergic manifestations in man are similar to the effects of administered histamine;[33] (4) a histamine-like substance is actually released during allergic states in man;[34] (5) antihistaminic agents clinically may be used for the control of many symptoms of allergy.

These similarities of action form the basis for the widely accepted view that histamine is an important agent in allergic conditions. However, this belief is not universal. Wells, in 1921[82], found certain discrepancies between histamine and anaphy-

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lactic shock: histamine fails to desensitize animals or tissues, although it does produce strong reactions in the uterine muscle strip which has been desensitized; it produces neither the temperature reactions nor the changes in blood coagulability seen in anaphylaxis; and its effects are not augmented by quinine, whereas those of anaphylaxis are. In turn, these and other objections have been answered in great detail by proponents of the histamine theory. The literature in this regard is voluminous and has been completely reviewed by various authors.[62,9,60,71]

The bronchospastic potentialities of histamine were recognized by the earliest investigators,[21] but it was not until 1921 that Schenk[64] demonstrated respiratory distress, attributed to broncho-constriction, after administration of large doses of this agent. In 1927, Weiss, Robb and Blumgart[79] studied the velocity of the circulation of the blood in man by means of injections of histamine. In the course of this work they induced dyspnea, with the signs and symptoms of bronchial asthma, in several subjects with a past history of asthma. They likewise induced dyspnea in patients suffering from chronic bronchitis, emphysema, or cardiac asthma, as well as in a few individuals with congestive heart failure. The definite bronchospastic action of histamine in such individuals was confirmed in another study by Weiss, Robb and Ellis.[80] This bronchospastic action of histamine in individuals with various types of respiratory disease has been used diagnostically as a "respiratory function test" by Schlösser[66] and Müller[58] in differentiating varieties of dyspnea.

Dautrebande and his co-workers in Europe have long been interested in the aerosol route for topical application of therapeutic substances to the inner surface of the lungs and, by means of bronchopulmonary absorption, to the general body economy. In 1940 they used histamine aerosols to demonstrate the possibility of this transpulmonary absorption,[23] and, in the following years, they studied in great detail the action of aerosolized histamine upon the lungs.[24,25,26]

Dautrebande's complex techniques for aerosol production and administration and his methods of measurement of pulmonary function differ from those we have used. He finds that three inhalations of a 1 per cent histamine aerosol, as produced in his apparatus, lead to an increase in the efficiency of respiration and in "pulmonary volume," namely, to bronchial relaxation. On the contrary, we have produced, in occasional subjects, a significant drop in vital capacity with only one inhalation of a hand-bulb-produced aerosol of a 0.5 per cent solution of histamine base. Three inhalations of this solution will produce bronchospasm in many of our subjects.

Curry, in 1946,[17,18] administered histamine diphosphate by intravenous and intramuscular routes both to normal subjects and to those suffering from hay fever and asthma. The resulting changes in respiratory function were measured and determined as alterations in the vital capacity. He found that histamine in the doses employed produced no significant drop in vital capacity in normal subjects or in hay fever patients, but it did cause significant decrease in vital capacity in most asthmatics.

If histamine is the offending agent in allergic reactions, then, theoretically, it might be possible to use it in minute and gradually increasing doses in the same manner as allergenic extracts are used, namely, as a therapeutic hyposensitization measure. Favorable results from such an approach to the treatment of asthma were reported by Ramirez and St. George in 1924,[61] Dzinich in 1935,[37] Farmer in 1940[41] and 1941,[42] and others. However, the apparent lack of success with this preparation in the hands of most investigators led to the subsequent use of histamine-protein conjugates; these, too, are now thought to be essentially valueless.[43]

Histamine is destroyed *in vitro* by various tissue extracts which have been considered to contain histaminase, an enzyme which, too, has been suggested as a therapeutic possibility; it has also been found largely inert clinically.[16] Best, who originally described this enzyme, feels that his group and other workers "have failed to show that the intravenous or intramuscular administration of histaminase has any effect on the histamine present in the body or on that given by injection."[10]

ACETYLCHOLINE

Acetylcholine, synthesized by Baeyer in 1867, came into experimental and clinical use as a result of the demonstration by Loewi of its role as the chemical mediator of vagal impulses ("Vagusstoff")—at least as far as the heart was concerned.[52] Acetylcholine shares certain physiological properties with histamine: it is widely distributed in living tissues; it is the acetyl ester of a base (choline) and is thus chemically, though distantly, related to histamine, also an organic base; and it is, as histamine has been thought to be, destroyed *in vivo* by an enzyme, cholinesterase. The action of cholinesterase may be prevented by physostigmine (eserine) or its derivative (e.g. neostigmine). While the physiological role of histamine remains obscure, acetylcholine has a vital function in the normal organism. It is the chemical mediator of nervous impulses across synaptic junctions in the entire nervous system, and it also serves as the chemical mediator effecting the passage of nervous impulses from motor nerve endings to effector organs in the parasympathetic nervous system as well as in the central nervous system.

In general, the actions of acetylcholine may be divided into those which are similar to the effects of stimulation of the parasympathetic nervous system (which may be simulated by muscarine) and those occurring within ganglia and at the motor endplates of striated muscle (similar to the effects of nicotine). The muscarinic actions of acetylcholine can be prevented or blocked, to a large extent, by atropine; the nicotinic effects can not. Administration of acetylcholine to man leads to phenomena largely of the muscarinic type: flushing of the head and upper part of the body, throbbing in the head, palpitation, sweating, lachrymation, substernal constriction, and, when given in larger doses, to nausea and vomiting and loss of urinary and rectal sphincter control. The intravenous administration of moderate doses of acetylcholine has little or no effect on pulse and blood pressure;[39] larger doses produce bradycardia and hypotension.[14]

Acetylcholine is a markedly unstable compound, and is itself seldom employed clinically. Two derivatives are available, carbaminoylcholine and acetyl-beta-methylcholine. The latter is more usually employed as a parasympathicomimetic agent. It produces effects closely similar to but not identical with those of acetylcholine.[15] So far as cardiovascular and general responses are concerned, acetyl-beta-methylcholine is 200 times more potent than the parent substance.[8] The relationship of these substances to one another and to the transmission of the nervous impulse is the subject of a series of Croonian lectures by Fraser.[44]

The first suggestion that bronchial asthma might represent an imbalance of the autonomic nervous system with an abnormal preponderance of vagal impulses was made in 1909 by Eppinger and Hess,[40] who characterized asthma as an example of "pathological vagotonia." In 1921 Alexander and Paddock[3] afforded some support to this theory. They found that patients with bronchial asthma were more sensitive to pilocarpine, a drug which simulates the action of the parasympathetic nervous system, than were normal individuals. In addition, the administration of 3 mg. of pilocarpine subcutaneously provoked asthmatic breathing in ten of twenty asthmatic subjects, whereas it had no such effect in normal subjects.

While studying the effects of intravenous administration of acetylcholine to normal men, Ellis and Weiss in 1932[39] found that "frequently the subjects experienced a sensation of substernal constriction with some difficulty in inspiration and a slight dry cough. No true wheezing was noted." These findings were confirmed for acetylcholine by Carmichael and Fraser,[14] and for acetyl-beta-methylcholine by Comroe and Starr.[15] In the course of further studies with acetyl-beta-methylcholine, Starr et al, in 1933,[72] found that in one subject with a history of asthma, parenteral administration of this agent led to the development of "a typical asthmatic attack" lasting three minutes. Similar but milder episodes were produced in other known asthmatics after oral administration of acetyl-beta-methylcholine, as well as in one elderly patient

not previously known to have bronchial asthma.[73] In the next year, Villaret and his co-workers[76] reported bronchospasm and rhinorrhea in asthmatics induced by the subcutaneous administration of 20 to 40 mg. of acetyl-beta-methylcholine. These episodes, some of which were quite severe, could be terminated at will by atropine. It is noteworthy that coryza could not be reproduced in a patient with allergic rhinitis. No similar respiratory effects were noted after the administration of these doses of acetyl-beta-methylcholine to normal individuals. Villaret's group was sufficiently impressed with these phenomena to recommend the use of acetyl-beta-methylcholine as a diagnostic test in differentiating bronchial asthma from hysterical hyperpnea. Simultaneously, Hurtado and Kaltreider,[47] studying the total pulmonary capacity, induced decreases in vital capacity of 700 and 760 c.c. after administration of 15 and 30 mg. of acetyl-beta-methylcholine intramuscularly to two healthy young adult subjects. These decreases in vital capacity were associated with substernal constriction and difficult breathing.

This gradually accumulating body of evidence, tending to involve acetylcholine as the chemical mediator of allergic as well as of nervous phenomena, led to the study by Wenner and Buhrmester of the level of acetylcholine in the blood of rabbits in anaphylactic shock.[83] These investigators showed that acetylcholine was present in the blood of sensitized and of shocked rabbits, although it was not found in normals. Physostigmine was not used, and the demonstration of acetylcholine in blood when cholinesterase activity has not thus been eliminated must mean that higher levels were actually present. The presence of histamine in the blood of similarly prepared animals has also been demonstrated, but the results are conflicting.[78,62,35,36] Alexander, discussing the paper of Wenner and Buhrmester,[83] felt that all the peripheral manifestations of anaphylaxis and allergy might be reproduced by stimulation of the parasympathetic nervous system. The results of this investigation were confirmed in human asthmatics by Parrot.[59] Fraser[44] reported definite, fluoroscopically observed, constriction of the smaller bronchi when 25 mg. of acetyl-beta-methylcholine were administered intramuscularly in the course of bronchography with iodized oil.

In 1940, Moll [57] carefully studied the effect of the subcutaneous administration of acetyl-beta-methylcholine in asthmatic subjects. To quote Moll, "the attack produced by acetyl-beta-methylcholine is indistinguishable from a spontaneous attack of asthma." Using doses of 10 to 20 mg., he was able to produce some degree of bronchospasm in almost every asthmatic patient; very few normal subjects experienced any disturbance of respiratory function after such injections. Moll felt that in asthma "it is the bronchial nervous system which is abnormally sensitive and not the whole parasympathetic nerves (*sic*) as Eppinger and Hess maintained in their theory of vagotonia."[47] He believed that this abnormal hypersensitivity of the bronchial tree to vagal impulses was the result of previous lung damage that might have occurred in cases of asthma following pneumonia, pertussis, et cetera. Villaret et al,[77] in animal experiments, found that the susceptibility of the tracheobronchial tree to carbaminoylcholine was greatly increased by inhalation of irritant vapors.

Moll refrained from assigning acetylcholine a causal role in bronchial asthma because atropine, which effectively antagonizes the effects of administered acetylcholine on the bronchial tree, is of limited clinical value in the treatment of asthma.[57] This apparent paradox has been noted in other experiments on the parasympathetic nervous system. Dale and Gaddum in 1930[22] found that the blocking action of atropine upon the muscarinic effects of acetylcholine existed in three degrees. In some cases it was complete; in others, the effects of administered acetylcholine could be prevented while those of nerve stimulation were not affected; and in still other instances, atropine apparently had no blocking effect whatever. Such phenomena have been observed in the gastrointestinal tract, in the tissues innervated by the parasympathetic fibers of the chorda tympani, and in the contracture of denervated striated muscle after stimulation of parasympathetic vasomotor fibers. It was postulated that the

action of atropine might be considered as producing a barrier preventing the access of acetylcholine to the effector organ. The effect of atropine will then vary as the acetylcholine is liberated outside, partly within, or wholly within this barrier. Despite the lack of clinical efficacy of atropine, it is thus possible that acetylcholine may be the agent responsible for the bronchospasm of bronchial asthma.

In this connection, the effect of atropine on anaphylactic shock is of importance. However, this a debatable subject. Hill and Martin,[46] in their classic review of experimental studies of nonspecific inhibition of anaphylactic shock, list atropine as one of the eighteen substances which had been shown to have a definite inhibitory action on anaphylactic phenomena. Kokas et al[48] were later unable to confirm this view.

While working with dogs prepared so that the trachea was interrupted and respiration took place through a tracheal cannula, Binet and Burstein in 1940[11] found that irritation of the nasal mucosa by fumes of ammonia, which did not come into contact with the trachea or lower respiratory passages, led to marked constriction of the bronchi and bronchioles. This reflex was exaggerated by physostigmine and was abolished by section of the vagi. This demonstration of one type of bronchospasm, definitely of reflex vagal origin, lends collateral support to the acetylcholine theory of the pathogenesis of asthma. A more complete study of the nasal passages is included in a report on the etiology of dyspnea in the hay fever patient.[6]

The bronchospastic potentialities of choline derivatives have been further investigated by Dautrebande and his group in their continuing study of the properties of various aerosols.[24,26,27,62] They have been particularly interested in the effects of aerosols of solutions of carbaminoylcholine. This has become their standard method for the production of bronchospasm, which they have been able to neutralize by injections of atropine and by aerosols of amphetamine. Dautrebande and Phillipot in 1941[28] further demonstrated that the administration of amphetamine will protect a human subject against the bronchospastic action of a subsequent dose of carbaminoylcholine aerosol.

Tiffeneau and Beauvallet in 1944[74] and 1945[75] demonstrated that inhalation of 1 per cent acetylcholine aerosol produces no modification of respiration in a normal subject; but in individuals with respiratory insufficiency, it provokes a diminution of vital capacity of 700 to 1000 c.c., even when the patient is asymptomatic and when other tests reveal no evidence of disability. They suggested that this response might be used diagnostically and as a measurement of the degree of disability from which a given subject might be suffering. They were able to show that acetylcholine administered in this way is totally destroyed in the lung and thus produces no systemic effects, thereby rendering their proposed test a fairly innocuous one.

Curry in 1947[18] reported the effect of intravenous and aerosol administration of acetyl-beta-methylcholine on the vital capacity of both normal subjects and patients with hay fever and asthma. He was able thus to produce decreases in vital capacity in eleven patients with hay fever and in twenty-seven with asthma. Normal subjects did not respond.

As with histamine, attempts have been made to treat allergic individuals by graded injections of acetyl-beta-methylcholine. Logue and Laws in 1942[53] reviewed the previous literature and presented their own experiences with twenty patients. They concluded that such therapy was of no material benefit.

The possible role of cholinesterase in the pathogenesis of bronchial asthma requires further study. A few isolated observations of Milhorat[56] indicate that the level of serum cholinesterase in asthmatics may be higher than normal. This would seem to lead to more rapid destruction of acetylcholine than normal, and thus, toward bronchial relaxation rather than asthma. Cholinesterase has not been available for therapeutic trial in asthmatic patients.

HISTORICAL DEVELOPMENT OF PROTECTION STUDY TECHNIQUES IN THE INVESTIGATION OF BRONCHOSPASM

From the time of the first data linking the manifestations of allergy in man to those of anaphylaxis in animals, many investigators have attempted to find experimental procedures or therapeutic substances which might modify anaphylactic reactions and thus be of clinical value in the treatment of the allergic patient. In 1932, Hill and Martin[46] reviewed over 150 such techniques, ranging from adrenalectomy to the use of mud from therapeutic springs. Epinephrine and atropine were among the substances which these authors felt were of value in inhibiting anaphylactic shock; quinine was thought to intensify such phenomena. Edlbacker, Jucker and Baur in 1937[38] investigated the protecting ability of various amino acids against the effect of histamine on guinea pig intestinal strips *in vitro*. They found histidine, arginine, and cysteine to be active in this regard. Tremendous doses are necessary, however, and these compounds are of little clinical value as antihistaminic agents. Ackermann and Wasmuth in 1939[2] confirmed these studies and added several new protecting agents, derivatives of arginine and guanidine. Again, toxic doses were necessary, but these authors were able to protect dogs against the hypotensive effects of subsequently administered histamine with some of their compounds. No action against acetylcholine could be demonstrated.

Binet and Bochet in 1941,[12] using aerosols, were able to protect dogs against the bronchospastic effects of histamine and of carbaminoylcholine with aerosols of epinephrine; aerosols of atropine also relaxed the spasm induced by carbaminoylcholine. Halpern[45] investigated the antihistaminic agent N'-phenyl-N'-benzyl-N-dimethylethylenediamine (Antergan) in 1942. Pre-treatment of guinea pigs with this substance prevented the occurrence of asphyxia after subsequent exposure to histamine aerosols. Schaumann[63] in 1943 devised a standard technique (in terms of the latent period of development of bronchospasm after exposure to histamine aerosols) for measuring the protecting effect of various agents against histamine-induced bronchospasm in guinea pigs. He found this time interval (standard protection time) to be prolonged by various ephedrine and epinephrine derivatives, of which dihydroxyephedrine was the most potent. Atropine and papaverine were inert.

In 1945 and 1946, Loew, Kaiser and More [49-51] studied extensively the protecting effect of various drugs against atomized histamine in guinea pigs. They devised a technique by which 90 to 100 per cent of experimental animals succumbed to asthma induced by the inspiration of atomized histamine solutions in closed chambers. They then tested the ability of various drugs to protect against this bronchospasm by intraperitoneal administration fifteen minutes prior to exposure of the animals to the histamine spray. Various agents provided significant reduction of mortality. Loew et al proposed an "activity index" for the description of the relative antihistaminic potency of these substances. This index denotes the ratio of the minimum dose of the drug in question exhibiting a significant protecting action to the dose of theophylline ethylenediamine which produces the same effect. Thus aminophyllin has an index of 1.0. Epinephrine with an activity index of 500 was the most potent agent employed; diphenhydramine hydrochloride (Benadryl) with an index of 33, meperidine hydrochloride (Demerol hydrochloride) with an index of 8, atropine sulfate with an index of 3, and papaverine hydrochloride with an index of 2, also provided significant protection. Many substances had no protecting action; these were 2-amino-heptane sulfate (Tuamine sulfate), beta-diethylaminoethyldiphenyl acetate hydrochloride (Trasentin), beta-diethylaminoethylfluorene-9-carboxylate hydrochloride (Pavatrine), gamma-diethylamino-beta, beta-dimethylpropyl-dl-tropate phosphate (Syntropan), procaine, 2-butoxy-4-(beta-diethylaminoethylamido) carboxyquinoline hydrochloride (Nupercaine), pentobarbital, morphine and ergotamine. Perplexingly, ephedrine, as well as physostigmine, seemed to potentiate this experimental asthma. The paradox-

ical action of ephedrine was assigned to its stimulating effect on respiration, resulting in the inspiration by the guinea pigs of more of the histamine spray, and thus producing more severe bronchospasm than was provoked in the control animals. The lack of similar potentiation of bronchospasm by caffeine sodium benzoate, an even more powerful respiratory stimulant, is as yet unexplained. The potentiation with physostigmine "may be referable to the potentiation of the systemic effects of acetylcholine which would be liberated in increased quantities during asphyxial convulsions."[50]

Simultaneous with these pharmacological studies, Dautrebande and his collaborators [26,27,31,32] demonstrated the protecting ability of intravenous atropine against aerosols of carbaminoylcholine in dogs and the similar protecting action of amphetamine aerosols in human subjects. By 1942, these investigators had studied a long series of bronchospastic and bronchodilator substances and had demonstrated the antagonistic and protecting actions of each class of drugs on the other. They have employed the following bronchodilator agents (in order of increasing potency): epinephrine, dioxy-norephedrine (Corbasil), paraoxyphenylethanolmethylamine (Synephrin), oxyphenylaminopropane (Veritol), ephedrine, alphahydroxy-beta-methylaminopropylbenzene (Ephetonine), oxyephedrine (Suprifene), benzyl ether of benzylethylmethylamine (Arilin), phenylmethylaminopropane (Pervitin), phenylaminopropane (amphetamine), meta-oxyphenylethanolmethylamine (Neo-Synephrine), and isopropylepinephrine (Aleudrin or Isuprel). Segal and Beakey [67,68] were the first in this country to describe the clinical value of Isuprel. Atropine aerosols of themselves were found to have little action in normal subjects, but were very efficacious in releasing the bronchoconstriction produced by aerosols of pilocarpine or of choline esters. Dautrebande and his associates have made use of carbaminoylcholine and, to a lesser extent, of histamine, pilocarpine, acetyl-beta-methylcholine and acetylcholine itself[26] as bronchospastic agents.

Tiffeneau and Beauvallet,[75] in their study of the use of aerosols of acetylcholine to measure the degree of respiratory insufficiency in disabled individuals, made use of the complete protecting effect of atropine aerosols against acetylcholine in the detection of malingerers, who might then react to subsequent acetylcholine aerosols, whereas truly asthmatic individuals would not.

Curry, in 1946,[19] using serial determinations of the vital capacity as a measure of bronchoconstriction, as did Hurtado and Kaltreider,[47] studied the protecting action of various substances on the bronchospasm produced in asthmatic subjects by intravenous administration of histamine. He investigated diphenhydramine hydrochloride (Benadryl), tripelennamine hydrochloride (Pyribenzamine), atropine, aminophyllin, epinephrine, and ephedrine. Both of the antihistaminic agents studied were found to have protecting ability against histamine. Atropine, too, was found to furnish complete protection against the bronchospasm produced by aerosols of histamine (one experiment), but it protected only partially against histamine administered intravenously. Theophylline ethylenediamine furnished "prompt and potent protection against the tracheobronchial effects of intravenous histamine."[19] Epinephrine and ephedrine administered intramuscularly were also effective against histamine. Curry concluded that "this method of study provides a means of measuring the bronchodilator activity of the various sympathicomimetic amines."[19] His technique yielded results in which data on individual patients could not be massed into statistically significant forms, and thus accurate comparison of various antihistaminic agents was not practicable.

As interest in the laboratory production of bronchospasm in susceptible individuals has grown, attempts have been made to induce such bronchospasm by means of allergens, and to avoid the controversial nature of the effects of histamine and of the choline esters. Lowell and Schiller[54,65,55] have recently demonstrated decreases in vital capacity in sensitive asthmatics after the administration of aerosols of pollen extracts. This and similar techniques give great promise for the future.

We have modified the techniques described above so that statistically valuable data may be produced and various agents used in the treatment of asthma be assayed.[69] We have employed, by aerosol as well as intravenous routes, histamine, acetyl-beta-methylcholine, and allergenic extracts as bronchospastic agents. Results obtained from the study of the first group of agents tested (parasympathicolytic substances) follow;[7] other reports are in preparation.[13,70] By means of this technique, we hope that an approach may be made to the fundamental problem of the pathogenesis of bronchial asthma and thus to its management on a rational basis.

METHODS

Various methods for measuring different aspects of pulmonary function have been used, such as measurement of reserve air, inspiratory and expiratory velocities, total pulmonary ventilation, and determination of vital capacity.[20] We have employed the last named method in the majority of our studies, and it has proved entirely adequate for our purposes. It is a simple procedure that requires no complicated apparatus or time-consuming calculations. A modification of the standard Benedict-Roth spirometer with a rapidly moving drum, equipped with a Reichert counter, was employed in many of the studies. In others, we employed the easily portable McKesson-Scott vital capacity apparatus, which is particularly useful when more than one subject is being studied at one time. Vital capacity determinations with either apparatus are identical.

Certain factors, including age, cough, general weakness, state of dentition, emotions, intelligence and co-operation, make widely separated determinations of vital capacity entirely unreliable. However, co-operative subjects can be trained to repeat vital capacity determinations which fall consistently within a relatively narrow range. It was usually possible, without undue selection of individuals, to train our asthmatic subjects so that decreases resulting from the administration of bronchospastic agents could be adequately evaluated. A further training period was necessary so that the subjects would be able to concentrate upon the expiratory effort of the vital capacity determination to the exclusion of the sometimes disturbing side reactions produced by administration of these agents. Side effects varied with the route of administration: intravenous injection produced the severest reactions; intramuscular administration, less intense but more prolonged reactions; and the aerosol route, only rare and slight reactions.

The intravenous route, as compared with the intramuscular, is more quantitative, constant, and predictable, and is therefore preferable.

The effect of intravenous administration of histamine or acetyl-beta-methylcholine begins fifteen or twenty seconds after its administration. The first effect is that of a disagreeable metallic taste (this sensation of taste makes positive that the injection was intravenous), accompanied by the beginning of a series of sensations related to vasodilatation and other cardiovascular phenomena. These responses reach their maximum in approximately forty-five to sixty seconds and consist of headache, flushing, palpitation and giddiness. Administration of acetyl-beta-methylcholine often produced salivation, lacrimation, and a sense of substernal constriction, whereas headache was not noted. Serial determinations of the vital capacity after the administration of either of these agents revealed that the maximum diminution in vital capacity occurs approximately thirty seconds after the intravenous administration of the bronchospastic substance. This drop was determined with stopwatch timing by having the patient perform vital capacities at specified intervals after injection. The most satisfactory intervals were found to be thirty seconds and then one, two, three, and five minutes after injection. We have repeatedly shown that a patient is capable of performing vital capacities at thirty second intervals for several minutes without appreciable change. As previously noted, the maximum drop in vital

capacity is almost invariably seen thirty seconds after injection. Figure 1 depicts a typical response to the intravenous injection of a bronchospastic agent. The vital capacity usually returns to normal in one to five minutes; frequently, it returns to levels considerably higher than the original. This "rebound phenomenon" will be discussed

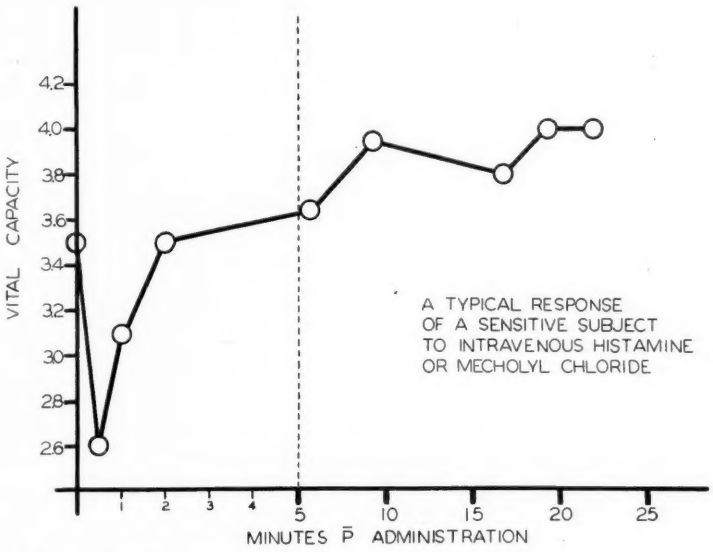

Fig. 1. A typical response of a sensitive subject to the intravenous administration of histamine or acetyl-beta-methylcholine.

below. After pre-treatment of the experimental subject with protecting agents, the return of the vital capacity to the resting level after injection of the bronchospastic substance was usually more rapid.

Histamine diphosphate solution (Abbott),* of which each c.c. represented 0.1 mg. of histamine base, was used. All doses of histamine are reported in terms of the base. The preparation of acetyl-beta-methylcholine chloride was that of Merck** (Mecholylchloride) and hereinafter will be referred to simply as "mecholyl." It was dissolved in sterile physiological saline to a final concentration of 1.0 mg. per c.c. (doses of this substance are reported in terms of the chloride). The concentration of each substance was chosen so that the usual dose for intravenous administration would fall within the range of 0.1 to 0.4 c.c., and thus a quick and accurately timed injection was made possible. Fresh solutions of mecholyl, stored in sterile rubber-capped vials and refrigerated when not in use, were prepared weekly. The marked instability of the choline ester linkage makes such precautions necessary. It is an accepted fact that the blood cholinesterase rapidly inhibits the action of administered acetylcholine. This suggested the possibility that drawing blood back into the syringe prior to intravenous injections might lead to the destruction of some of the mecholyl. Consequently, tests were performed in which the amount of mecholyl known to cause a drop in vital capacity was mixed with the patient's blood for ninety seconds and then reinjected. No alteration in the previously determined drop in vital capacity

*Kindly supplied through the courtesy of Abbott Laboratories, North Chicago, Illinois.
**Kindly supplied through the courtesy of Merck and Company, Rahway, New Jersey.

occurred, and it was apparent that immediate hydrolysis by the esterase was not sufficient to alter the studies in question.

New patients generally first received intramuscular injections of 0.06 mg. of histamine or 0.1 mg. of mecholyl as test doses in order to detect any abnormal sensitivity; no such instance was demonstrated. The intravenous doses of histamine usually ranged from 0.01 to 0.04 mg. However, two subjects reacted consistently to 0.005 mg., and one subject to 0.002 mg. The highest dose used in a protection study has been 0.06 mg., although greater amounts have been administered during the course of our investigations. In general, a dose of mecholyl sufficient to produce a significant drop in vital capacity was attended by much less severe side effects than an equally effective dose of histamine. The doses of intravenous mecholyl employed usually ranged from 0.05 to 0.4 mg. Sometimes the severity of the side reactions produced by histamine necessitated discontinuing the experiment before a dose capable of producing a decrease of the vital capacity could be given. Side reactions to mecholyl were much better tolerated. Occasionally the critical range of bronchospastic doses was very narrow and resulted in the administration of excessive amounts even with very small increments. The most prominent symptom from overdoses of histamine usually was incapacitating headache. However, excessive doses of mecholyl produced more alarming effects. Approximately twenty-five seconds after such an injection the patient seemed to lose consciousness. A vacant stare appeared, followed by momentary cessation of respiration and clonic movements of the arms and legs. The entire reaction lasted only ten to fifteen seconds. A solution of atropine sulfate was always kept ready, in a syringe, for immediate intravenous administration, but no reaction long enough to allow its use occurred. Patients later described such reactions as "going numb all over" with a sense of constriction in the chest and transitory inability to move the limbs. The clinical features of these reactions suggest transitory asystole.

The aerosol route for administration of bronchospastic agents, and of therapeutic substances as well, has been employed extensively. In all instances we have made use of aerosols produced with the standard Vaponefrin† nebulizer. For uniformity, a standardized technique for aerosol administration has been devised. The nebulizer is held by the experimenter with its outlet orifice close to the patient's open mouth. The experimenter counts aloud, and at the count of "three" the nebulizer bulb is squeezed with maximal force as the patient simultaneously makes the deepest and most rapid inspiration possible, following which he holds his breath in inspiration for four or five seconds. The procedure is repeated at precisely ten-second intervals, until the desired number of inhalations has been given. The stopwatch is then immediately reset; further time intervals are thus calculated from the end of the last inhalation.

In contrast to the sequence of events following intravenous administration of histamine and of mecholyl, the effect of such agents given by the aerosol route is slower both in onset and in recovery. The maximum drop in vital capacity usually occurs one or two minutes after the last inhalation; in occasional instances it may not take place until three minutes thereafter. Recovery is usually complete within eight to ten minutes. A typical response of a sensitive subject to an aerosol of a bronchospastic agent is depicted in Figure 2. We have not observed the "rebound phenomenon" following the administration of histamine or of mecholyl by the aerosol route. Side-reactions are infrequent when bronchospastic agents are administered in this way, in contrast to their almost invariable occurrence, to some degree, after intravenous injection. Those side-effects which do occur are similar to the reactions already described, but much less severe.

Essentially, a protection study consists of the determination of the effect on vital

†Kindly supplied through the courtesy of the Vaponefrin Company, Upper Darby, Pennsylvania.

capacity of a bronchospastic agent before and at varying intervals after administration of a protecting drug.

A typical protection study was begun with a rest period of fifteen to twenty minutes; the patient sat quietly, and all constricting clothing was loosened. The vital

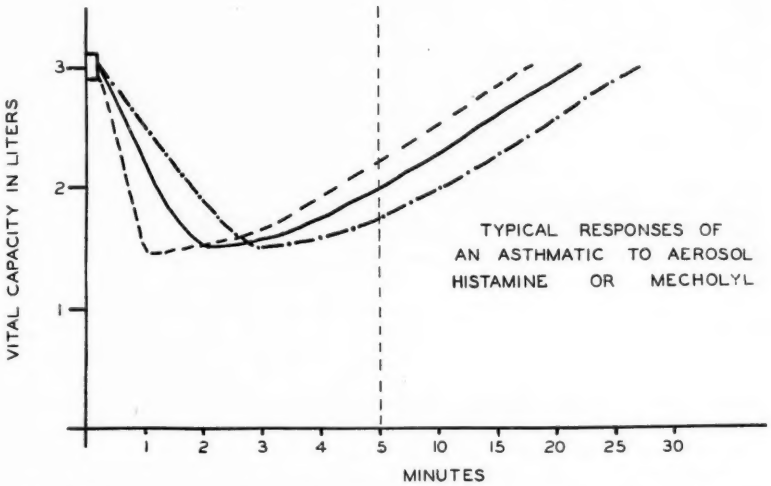

Fig. 2. Typical responses of asthmatic subjects to the administration of aerosols of histamine or acetyl-beta-methylcholine.

capacity was determined serially until several results were within plus or minus 100 c.c. The dose of bronchospastic agent required to produce a significant "control" drop in vital capacity was then determined. Such a significant drop was usually 1 to 2 liters, although sometimes it was necessary to accept slightly smaller decreases in those patients whose basal vital capacities were as low as 2 liters. In this determination, gradually increasing amounts of bronchospastic agent were administered every twenty to thirty minutes until a desirable decrease in vital capacity was obtained. In the case of histamine, the increments were 0.005 or 0.01 mg., and, in the case of mecholyl, 0.05 or 0.1 mg.

After the control drop for the day was established and verified at least once, the protecting drug was administered. Following this, vital capacities were again determined and followed by serial administration of the bronchospastic agent at intervals of not less than twenty minutes. Before each successive injection of the bronchospastic agent, three to five vital capacities were always determined at intervals of one to two minutes in order to reaffirm the basal vital capacity from which the amount of drop was to be calculated. The new "basal" vital capacities were sometimes several hundred c.c. higher than the original basal readings; this was due to the previously mentioned rebound phenomenon, to the therapeutic effect of the protecting agent, or perhaps to the bronchodilating effect of repeated forced expirations *per se*. The decrease in vital capacity, when the bronchospastic agent was readministered, was computed from this higher level, which was frequently maintained for a considerable period of time. Consequently, when protection was finally lost, i.e., when the decrease was equal to the control drop, the point to which the vital capacity fell might still be higher than even the original basal determinations. The loss of protection was usually verified by at least one further dose of histamine or mecholyl.

The sensitivity of the tracheo-bronchial tree to either of these substances varied in most subjects from day to day. It was minimal during asthma-free intervals and maximal during periods of active bronchospasm. Sensitivity did not usually vary within one day and thus did not affect the course of any one protection study in the vast majority of cases. In a few instances, a small dose of histamine or mecholyl appeared to potentiate the bronchospasm already present, over and above its usual effect. In such cases the vital capacity would fail to rise again over a considerable period of time, or it even would continue to decrease. Studies on subjects in active asthma, on whom an adequate control drop in vital capacity could be obtained, were as satisfactory as studies performed during periods of relative freedom from clinical asthma.

Serial increases in the dose of the bronchospastic agent caused increasing drops in vital capacity which were not always in proportion to the increment in dose. No cumulative effect was noted when the dose that caused a measurable decrease in vital capacity was repeated several times every twenty to thirty minutes. Repetition of the same dose several times during a seven-hour period showed that a refractory state of the tracheo-bronchial tree did not develop during the course of studies carried out for this length of time.

Vital capacity determinations were sometimes invalidated by cough due to the stimulus created by forced expiration or by the bronchospastic agent itself. If this effect was so marked as to preclude accurate, consistent determinations, the test was discontinued. It was possible, however, to carry out adequate protection studies on some subjects in whom a bronchitic element was present. Such patients often experienced a marked decrease in cough after the protecting agent was administered. One protection was established, proper spacing of basal readings, so as not to excite the cough reflex, was no longer necessary. Another interesting observation in such patients was the marked increase in vital capacity and decrease in cough that frequently occurred during the course of obtaining the basal readings. Apparently, the act of forced expiration into the apparatus produced a positive pressure, which was exerted backwards into the tracheo-bronchial tree as an internal distending force. Consequently, the vital capacity often reached a figure much higher than the determinations recorded when the subject first arrived at the laboratory. Care had to be taken that studies were not begun until the vital capacity had been maintained consistently over several recordings.

Data, describing the degree of protection afforded by a given protecting agent against a bronchospastic drug, are derived from these experiments. *We have repeatedly seen that any one protection study in a single individual may have little general applicability.* We have attempted, therefore, to determine an algebraic equation by which the degree of protection could be expressed in terms applicable to many subjects, so that the data might be subjected to some degree of statistical analysis. The decrease in vital capacity produced by a given dose of histamine or of mecholyl varies greatly from individual to individual, but remains constant in the same individual for the period of one protection study. During a period of protection, the decrease in vital capacity produced by the same dose of bronchospastic agent will, by definition, be less than the control drop. We have considered the percentage difference between these two values to be a measure of protection:

$$P = \frac{C - E}{C} \times 100$$

where P is the degree of protection in per cent, 100 per cent indicating absence of any decrease in vital capacity after the administration of histamine or of mecholyl; C is the control drop in vital capacity produced by an injection of the same quantity of the bronchospastic agent before administration of the protecting drug; and E repre-

sents the decrease similarly produced at any given time after the protecting drug has been administered.

Accurate evaluation of protection demands that the control drop in vital capacity exceed 1,000 c.c. We prefer to work within the range of 1,200 to 1,600 c.c. When, for example, 1,200 c.c. is achieved as the control drop, a later decrease of 800 c.c. would appear to indicate a protection of 33 per cent:

$$\frac{1200 - 800}{1200} \times 100 = 33\frac{1}{3}\%$$

However, variations of plus or minus 100 c.c. both in the "basal" vital capacity and in the determination thirty seconds after an intravenous injection of the broncho-

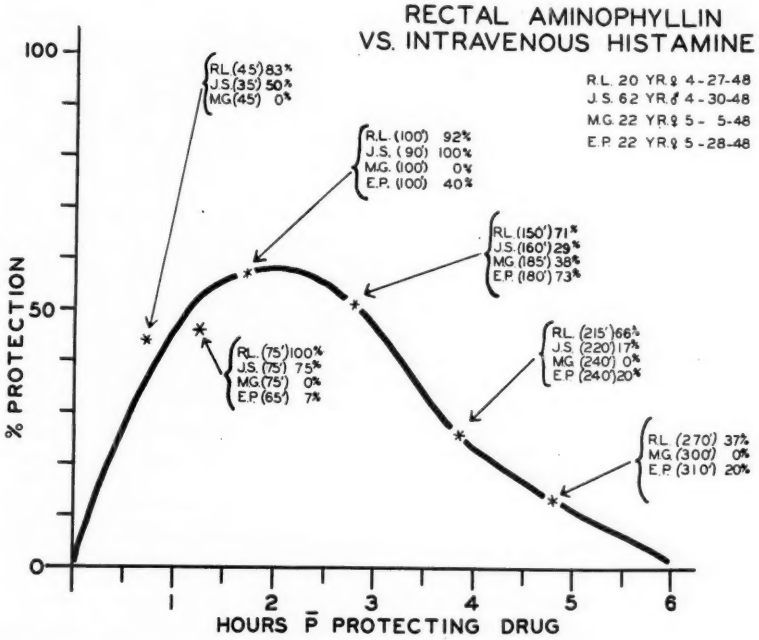

Fig. 3. A typical curve denoting the protecting capacity of a therapeutic substance, in this case aminophyllin given rectally, against the effects of a bronchospastic agent, in this case histamine given by vein. The curve represents the massed data from four protection studies, and thus is derived from a total of thirty individual doses of histamine including the control determinations.

spastic agent may produce, in any individual instance, a total difference of as much as 200 c.c. in the drop. An additional variation of 200 c.c. can be accounted for by virtue of the fact that the bronchospastic agent cannot be relied upon to produce precisely the same effect every time. The total range of variation, then, might be as much as 400 c.c.

If 600 to 800 c.c. is accepted as a control decrease in vital capacity, a later drop (after administration of a protecting drug) of only 200 to 400 c.c. might be considered to demonstrate considerable protection. Obviously, however, this would be open to serious error. Therefore, we have always attempted to attain control drops

of 1,200 to 1,600 c.c., and consider protection significant only when it is 40 per cent or more.

This transformation of data from vital capacity readings in cubic centimeters to percentage figures eliminates the dose of the bronchospastic agent from consideration as a variable factor. It also facilitates the statistical presentation of data obtained from experiments on several subjects into one curve of increased statistical probability. Such a graph, representing the massed data from four protection studies, derived from a total of thirty individual doses of a bronchospastic agent, is presented in Figure 3.

DISCUSSION AND COMMENTS

The results of these studies, with regard to the evaluation of a wide variety of drugs for the treatment of bronchial asthma, are to be reported in detail elsewhere. However, many important lessons have been learned, and much speculative and significant data has evolved in the actual performance of the tests.

The rebound phenomenon is very interesting. This consists of a rise in vital capacity above pre-injection levels after the drop produced by intravenous administration of a bronchospastic agent. This higher level, to which the vital capacity "rebounds," is usually not maintained, but generally settles back to the basal level (Fig. 1). In rare instances, however, the higher level *is* maintained, so that successive injections of bronchospastic agent, followed by successive "rebounds," have in this manner resulted in a gradually increasing vital capacity without any other form of treatment. This is a possible basis for the recommendations that the acute asthmatic state be treated with repeated minute injections of histamine.

This apparent paradox is not as yet completely explained. Acetylcholine in suitable doses leads to the liberation of epinephrine from the postganglionic cells which constitute the adrenal medulla. One may then postulate that the rebound phenomenon represents the effect of this released epinephrine. In the case of histamine, a somewhat similar argument is possible. It has been felt that the hypotensive effect of histamine is sufficient to excite the pressor receptors of the carotid sinus and aortic arch, leading to the outpouring of stored epinephrine from the adrenal medulla, as well as to compensatory vasoconstriction, and to acceleration of the heart rate. In this connection, it is certain that animals whose adrenals have been removed become more sensitive to histamine shock.[4]

These data should not be considered as supporting the discredited ideas of "desensitization" therapy with histamine. It is to be noted that we are dealing in this case with extremely short-lived experiments from the asthmatic standpoint and that the increment in vital capacity produced is maintained over a period of minutes or of a few hours at most. The deleterious effects of the administration of histamine or of acetylcholine to an individual in an actual attack of clinical asthma undoubtedly far outweigh its possible beneficial effects through this rebound phenomenon.

We have also observed what might be termed a "hyposensitization" to histamine and to mecholyl. Several patients, over the course of months of study, have displayed a decreased reactivity to comparable doses of the bronchospastic agents, particularly to histamine. This was paralleled by general improvement in the state of clinical asthma, yet the same decreased responsiveness was noted even during subsequent brief periods of reactivation of asthma. Hence, the decreased sensitivity to the bronchospastic drug could not possibly be ascribed only to the improved state of clinical bronchospasm. This is to be differentiated from the decreasing sensitivity noted over a short period when protection studies are carried out in a patient during the course of improvement from an acute asthmatic attack.

To what is this decreased sensitivity to be ascribed? Is it a true hyposensitization phenomenon? We are not prepared at this time, on the basis of available evidence, to invoke this mechanism. We feel that the general clinical improvement noted in so

many of our patients is due to many factors. These include constantly maintained reassurance (transference in the psychological sense), improvement in the patient's mental attitude towards his disease, education in therapeutic routines, and frequent breathing exercises and positive pressure applications entailed in the performance of vital capacity determinations over extended periods in the course of protection studies.

It is apparent that there is a difference in the mechanism by which histamine and mecholyl affect the tracheo-bronchial tree. The essential nature of the difference is not clear. Spontaneous observations by many patients disclosed a subjective response more closely paralleling clinical asthma with mecholyl than with histamine injections. Aerosol administration of either substance produces a condition even more closely simulating the clinical asthmatic state.

There has been a not inconsiderable number of patients who failed to develop bronchospasm and decreased vital capacity with fairly large doses of histamine. We have not observed any patient who failed to react to mecholyl at some time. One subject (J.R.), for example, received 0.09 mg. of histamine intravenously without decrease in vital capacity. Another (B.L.) required 0.08 mg. before a decrease in vital capacity of 800 c.c. occurred. Both patients reacted to moderate doses of mecholyl, although the former has subsequently become considerably less sensitive to mecholyl. The insensitivity to histamine may be only apparent in that bronchospasm may have been producible with even larger doses. However, the side-effects of such doses prohibit their use.

An interesting phenomenon has been the variation in histamine sensitivity with phases of the menstrual cycle (subject E.S.). She regularly displayed increased sensitivity just before and during each menstrual period. The obvious inference is that this is in some way explainable on the basis of variations in hormone levels themselves or on one or more of the secondary variations in metabolism paralleling the menstrual cycle.

Even more common have been variations in sensitivity of a seasonal nature. This has been especially apparent in studies performed on patients during and after the pollen season. Several patients so studied were quite sensitive to both histamine and mecholyl during the phase of active asthma. With the end of the pollen season, their sensitivities to both substances decreased markedly. For instance, subject I.D., during the pollen season, showed decreases of 700 c.c. and 1,300 c.c. from a basal vital capacity of 4,000 c.c. after intravenous doses of 0.03 mg. and 0.035 mg. of histamine, respectively. Some weeks later, 0.05 mg. failed to decrease her vital capacity from 4,400 c.c. During the pollen season, her vital capacity was likewise decreased from 4,300 c.c. to 3,000 c.c. with 0.4 mg. of intravenous mecholyl. After the pollen season, 0.4 mg., 0.5 mg. and 0.6 mg. intravenously decreased her vital capacity only 350 c.c., 500 c.c. and 800 c.c., respectively. During a subsequent attack of acute bronchitis, 0.35 mg. intravenously again decreased her vital capacity by 1,300 c.c.

In the above patient, as well as in every other patient studied, aerosols of histamine and mecholyl never failed to cause bronchospasm as evidenced by marked decreases in vital capacity. Subsequent reports will deal with the efficacy of various classes of agents in protecting against the bronchospasm induced by these methods.

SUMMARY

1. The history of histamine and acetylcholine derivatives in relation to the allergic state and more specifically to bronchial asthma is reviewed.

2. The evolution of the use of these substances for the induction of dyspnea and bronchospasm in subjects with bronchial asthma is traced.

3. With this technique a method of assay in man of the relative value of new and of accepted therapeutic agents for the relief of bronchial asthma has been

evolved. The development and present status of this technique is the subject of the present report.

4. We have outlined in detail the method of protection studies which we have employed and have devised a formula and method of recording wherein the results obtained may become statistically meaningful and of a general applicability.

5. This method of human assay may enable one to evaluate accurately any new therapeutic agent for the relief of bronchial asthma and further to correlate clinical observations with the physiopathology of the disease.

REFERENCES

1. Ackermann, D.: On the bacterial destruction of histidine. Ztschr. f. physiol. Chem., 65:504, 1910.
2. Ackermann, D., and Wasmuth, W.: The mode of action of histamine. Ztschr. f. physiol. Chem., 259:28, 1939.
3. Alexander, H. L., and Paddock, R.: Bronchial asthma: Response to pilocarpine and to epinephrine. Arch. Int. Med., 27:184, 1921.
4. Banting, F. G., and Gairns, S.: Suprarenal insufficiency. Am. J. Physiol., 77:100, 1926.
5. Barger, G., and Dale, H. H.: Chemical structure and sympathicomimetic action of amines. J. Physiol., 41:19, 1910.
6. Beakey, J. F., and Segal, M. S.: Relationship of the nasal passages to bronchial asthma (nasogenic asthma)—etiology of dyspnea in hay fever subject. (Submitted for publication).
7. Beakey, J. F.; Bresnick, E.; Levinson, L., and Segal, M. S.: Evaluation of therapeutic substances employed for the relief of bronchospasm. III. Anticholinergic agents. Ann. Allergy (in press.)
8. Best, C. H.; Dale, H. H.; Dudley, H. W., and Thorpe, W. V.: The nature of the vasodilator constituents of certain tissue extracts. J. Physiol., 62:397, 1927.
9. Best, C. H., and McHenry, E. W.: Histamine. Physiol. Rev., 11:371, 1931.
10. Best, C. H., and McHenry, E. W.: A note on histaminase Canad. M. A. J., 43:163, 1940.
11. Binet, L., and Burstein, M.: Bronchospasm, and bronchodilation produced via the aerosol route. Presse med., 48:348, 1940.
12. Binet, L., and Bochet, M.: Study on the absorption by the respiratory passages of medicated solutions administered in fine droplets. Bull. Mem. Soc. Med. Hop., Paris, 57:281, 1941.
13. Bresnick, E.; Beakey, J. F.; Levinson, L., and Segal, M. S.: Evaluation of therapeutic substances employed for the relief of bronchospasm. IV. Adrenergic agents. (In preparation.)
14. Carmichael, E. A., and Fraser, F. R.: The effects of acetylcholine in man. Heart, 16:263, 1933.
15. Comroe, J. H., Jr., and Starr, I.: Further studies on the pharmacology of acetyl-beta-methylcholine and the ethyl ester of beta-methylcholine. J. Pharmacol. & Exper. Therap., 49:283, 1933.
16. Council on Pharmacy and Chemistry: Preliminary report on histaminase: Torantil. J.A.M.A., 115:1019, 1940.
17. Curry, J. J.: The action of histamine on the respiratory tract in normal and asthmatic subjects. J. Clin. Investigation, 25:785, 1946.
18. Curry, J. J.: Comparative action of acetyl-beta-methylcholine and histamine on the respiratory tract in normals, patients with hay fever, and subjects with bronchial asthma. J. Clin. Investigation, 26:430, 1947.
19. Curry, J. J.: The effect of antihistamine substances and other drugs on histamine bronchoconstriction in asthmatic subjects. J. Clin. Investigation, 25:792, 1946.
20. Curry, J. J., and Lowell, F. C.: Measurement of vital capacity in asthmatic subjects receiving histamine and acetyl-beta-methylcholine. A clinical study, J. Allergy, 19:9, 1948.
21. Dale, H. H., and Laidlaw, P. P.: The physiological action of beta-iminazolyl-ethylamine. J. Physiol., 41:318, 1910.
22. Dale, H. H., and Gaddum, J. H.: Reactions of denervated voluntary muscle, and their bearing on the mode of action of parasympathetic and related nerves. J. Physiol., 70:109, 1930.
23. Dautrebande, L.; Philippot, E.; Nogarede, F., and Charlier, R.: General action of medications introduced by the transpulmonary route. C. R. Soc. belge de biol., seance du 27 April, 1940.
24. Dautrebande, L.; Philippot, P., and Stalport, J.: Therapeutic aerosols: Volumetric pneumography after some pharmacodynamic and toxic substances. Presse med., 50:569, 1942.
25. Dautrebande, L.; Philippot, E.; Charlier, R.; Stalport, J., and Dumoulin, E.: Therapeutic aerosols: VII. Variable action of histamine and caffeine on the respiratory mechanism depending on the dose. Arch. Internat. de Pharmacodyn. et de Therap., 71:109, 1945.
26. Dautrebande, L.: Therapeutic Aerosols: Technique, Physiology, and Therapeutic Application. Paris: Masson et Cie, 1946.
27. Dautrebande, L.: Philippot, E.; Nogarede, F., and Charlier, R.: Production of therapeutic aerosols; possibilities of therapeutic application. Bull. Acad. de med., Paris, 123:379, 1940.
28. Dautrebande, L., and Philippot, E.: Experimental attacks of asthma by aerosols of carbaminocholine in man and treatment by aerosols of phenylaminopropane. Presse med., 49:942, 1941.
29. Dautrebande, L.; Philippot, E.; Charlier, R.; Dumoulin, E., and Nogarede, F.: Study of therapeutic aerosols in man. Influence of inhalation of bronchodilators and bronchoconstrictors on the degree of efficiency of pulmonary respiration. Presse med., 49:87, 1941.
30. Dautrebande, L.; Philippot, E.; Charlier, R.; Dumoulin, E., and Nogarede, F.: Therapeutic aerosols. II. Available and unavailable pulmonary volumes. Influence of bronchodilator substances on the efficiency of pulmonary respiration in man. Arch. internat. de pharmacodyn. et de therap., 66:337, 1941.
31. Dautrebande, L.; Philippot, E., and Charlier, R.: Therapeutic aerosols. New demonstration of their general action. Experimental study of aerosols of carbaminocholine and of atropine. Presse med., 50:398, 1942.
32. Dautrebande, L.; Philippot, E.; Charlier, R.; Dumoulin, E., and Nogarede, F.: Therapeutic aerosols, IV. Arch. internat. de pharmacodyn, et de therap., 68:117, 1942.

33. Dragstedt, C. A.: The significance of histamine in anaphylaxis. J. Allergy, 16:69, 1945.
34. Dragstedt, C. A.: pp. 799-800 in Feinberg, S. M.: Allergy in Practise. Ed. 2. Chicago: The Year Book Publishers, Inc., 1946.
35. Dragstedt, C. A., and Gebauer-Fuelnegg, E.: Studies in anaphylaxis: the appearance of a physiologically active substance during anaphylactic shock. Am. J. Physiol., 102:512, 1932.
36. Dragstedt, C. A., and Mead, F. B.: The role of histamine in canine anaphylactic shock. J. Pharmacol. & Exper. Therap., 57:419, 1936.
37. Dziuich, A.: Treatment of allergic conditions with histamine. Klin. wchnschr., 14:1612, 1935.
38. Edlbacher, S.; Jucker, P., and Baur, H.: The influence of amino acids on the intestinal reaction to histamine. Ztschr. f. physiol. Chem., 247:63, 1937.
39. Ellis, L. B., and Weiss, S.: A study of the cardiovascular responses in man to intravenous and intra-arterial injection of acetylcholine. J. Pharmacol. & Exper. Therap., 44:235, 1932.
40. Eppinger, H., and Hess, L.: On the pathology of the vegetative nervous system. Ztschr. f. klin. med., 67:345, and 68:205, 1909.
41. Farmer, L.: Histamine in anaphylaxis and allergy. Bull. New York Acad. Med., 16:618, 1940.
42. Farmer, L.: The histamine treatment of allergic diseases. I. Asthma and vasomotor rhinitis. J. Lab. & Clin. Med., 26:802, 1941.
43. Feinberg, S. M.: Histamine and histamine agents: Their experimental and therapeutic status. J.A.M.A., 132,702, 1946.
44. Fraser, F. R.: The clinical aspects of the transmission of the effects of nervous impulses by acetylcholine Brit. M. J., 1:1249, 1293, 1349, 1938.
45. Halpern, B. N.: Synthetic antihistaminics. Studies on the chemotherapy of allergic states. Arch. internat. de pharmacodyn. et de therap., 58:339, 1942.
46. Hill, J. H., and Martin, L.: A review of experimental studies of nonspecific inhibition of anaphylactic shock. Medicine, 11:141, 1932.
47. Hurtado, A., and Kaltreider, N. L.: Studies of total pulmonary capacity and its subdivisions. VII. Observations during the acute respiratory distress of bronchial asthma and after the administration of epinephrine. J. Clin Investigation, 13: 1053, 1934.
48. Kokas, F.; Sarkady, L., and Went, S.: On the role of choline and histamine in the pathogenesis of anaphylactic shock. Arch. f. exper. Path. u. Pharmakol., 187:479, 1937.
49. Loew, E. R.; Kaiser, M. E., and Moore, V.: Synthetic benzhydrylamine ethers effective in preventing fatal experimental asthma in guinea pigs exposed to atomized histamine. J. Pharmacol. & Exper. Therap., 83:120, 1945.
50. Loew, E. R., and Kaiser, M. E.: Alleviation of anaphylactic shock in guinea pigs with synthetic benzhydryl alkamine ethers. Proc. Soc. Exper. Biol. & Med., 58:235, 1945.
51. Loew, E. R.; Kaiser, M. D., and Moore, V.: Effect of various drugs on experimental asthma produced in guinea pigs by exposure to atomized histamine. J. Pharmacol. & Exper. Therap., 86:1, 1946.
52. Loewi, O.: The Humoral Transmission of Nervous Impulse. The Harvey Lectures: delivered under the auspices of the Harvey Society of New York, 1932-1933. Baltimore: Williams and Wilkins Co., 1934.
53. Logue, R. B., and Laws, C.: Mecholyl desensitization in the treatment of asthma. J. Allergy, 13:414, 1942.
54. Lowell, F. C., and Schiller, I. W.: Reduction in the vital capacity of asthmatic subjects after exposure to aerosolized pollen extracts. Science, 105:317, 1947.
55. Lowell, F. C., and Schiller, I. W.: Measurement of changes in vital capacity as a means of detecting pulmonary reactions to inhaled aerosolized allergenic extracts in asthmatic subjects. J. Allergy, 19:100, 1948.
56. Milhorat, A. T.: The cholinesterase activity of the blood serum in disease. J. Clin. Investigation, 17:649, 1938.
57. Moll, H. H.: The action of parasympathetic-mimetic drugs in asthma. Quart. J. Med. 9:229, 1940.
58. Mueller, P.: Practical application of the respiratory test by means of histamine. Deutches Tuberk.-Bl., 12:267, 1938.
59. Parrot, J. L.: Tissue hormones in pathology: Attempts at clinical use. Paris med., 1:497, 1938.
60. Rackemann, F. M.: Report on medical progress: Allergic diseases, with special reference to histamine and acetylcholine. New England J. Med., 222:674, 1940.
61. Ramirez, M. A., and St. George, A. V.: A contribution to the etiology of asthma. M. J. & Rec., 119:71, 1924.
62. Rocha e Silva, M.: Recent advances concerning the histamine problem. J. Allergy, 15:399, 1944.
63. Schaumann, O.: Pharmacological studies on histamine asthma in guinea pigs. Chem. zentralbl., 1:2701, 1943.
64. Schenk, P.: On the effects of histamine on the human organism. Arch. f. exper. Path. u. Pharmakol., 89:332, 1921.
65. Schiller, I. W., and Lowell, F. C.: The effect of drugs in modifying the response of asthmatic subjects to inhalation of pollen extracts as determined by vital capacity measurements. Ann. Allergy, 5:564, 1947.
66. Schloesser, J.: A respiratory function test using histamine. Ztschr. f. Tuberk., 78:225, 1937.
67. Segal, M. S., and Beakey, J. F.: The use of isuprel for the management of bronchial asthma. Bull. New England. Center, 9:62 (April) 1947.
68. Segal, M. S., and Beakey, J. F.: Management of bronchial asthma; the use of 1-(3′, 4′-dihydroxyphenyl)-2-isopropylaminoethanol. Ann. Allergy, 5:317 (July-August) 1947.
69. Segal, M. S., Beakey, J. F.; Bresnick, E., and Levinson, L.: Evaluation of therapeutic substances employed for the relief of bronchospasm, preliminary note. Bull. New England. Center, 10:21, 1948.
70. Segal, M. S.; Levinson, L.; Bresnick, E., and Beakey, J. F.: Evaluation of therapeutic substances employed for the relief of bronchospasm. V. Aminophyllin. (In preparation.)
71. Selle, W. A.: Histamine, its physiological, pharmacological, and clinical significance. Texas Rep. Biol. & Med., 4:138, 1946.
72. Starr, I., Jr.; Elsom, K. A.; Reisinger, J. A., and Richards, A. N.: Acetyl-beta-methylcholine. I. The action on normal persons; with a note on the action of the ethyl ether of beta-methylcholine. Am. J. M. Sc., 186:313, 1933.

73. Starr, I., Jr.: Acetyl-beta-methylcholine. III. Its action on paroxysmal tachycardia and peripheral vascular disease with a discussion of its action in other conditions. Am. J. M. Sc., 186:330, 1933.
74. Tiffeneau, R., and Beauvallet, E. T.: Role of the intrapulmonary destruction of acetylcholine. Local and general effects of acetylcholine aerosols. C. R. Soc. Biol., 138:747, 1944.
75. Tiffeneau, R., and Beauvallet, M.: Test of bronchoconstriction and bronchodilatation by aerosols. Use in detection, measurement and control of chronic pulmonary insufficiency. Bull. Acad. de med., Paris, 129:165, 1945.
76. Villaret, M.; Vallery-Radot, P.; Justin-Besancon, L., and Claude, F.: Preliminary research: On the attacks produced in certain asthmatic subjects by certain choline esters. C. R. Soc. Biol., 116:1343, 1934.
77. Villaret, M.; Vallery-Radot, P.; Justin-Besancon, L., and Claude, F.: Experimental asthmatiform attacks, provoked by the administration of vagomimetics, after pulmonary irritation. C. R. Soc. Biol., 124:1368, 1937.
78. Watanabe, K.: Quantitative studies of the content of intestine-contracting material in lung and liver of guinea pigs in a state of sensitization and in anaphylactic shock. Ztschr. f. Immunitatsforsch. u. exper. therap., 72:50, 1931.
79. Weiss, S.; Robb, G. P., and Blumgart, H. L.: The velocity of the blood flow in health and disease as measured by the effect of histamine on the minute vessels. Am. Heart J., 4:664, 1929.
80. Weiss, S.; Robb, G. P., and Ellis, L. B.: The systemic effects of histamine in man, with special reference to the responses of the cardiovascular system. Arch. Int. Med., 49:360, 1932.
81. Weiss, S., and Ellis, L. B.: The comparative effects of the intravenous administration of acetylcholine and acetyl-beta-methylcholine. J. Pharmacol. & Exper. Therap., 52:113, 1934.
82. Wells, H. G.: Present status of problems of anaphylaxis. Physiol. Rev., 1:44, 1921.
83. Wenner, W. F., and Buhrmester, C. C.: Potassium and acetylcholine of the blood of rabbits in anaphylactic shock. J. Allergy, 9:85, 1937.

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15. Piness, G.; Miller, H., and McMinn, H. E.: Botanical survey of Southern California in relation to the study of allergic diseases. Bull. So. Calif. Acad. Sc., 25: (Part 2) 37, 1926.
16. Rydberg, P. A.: North American Flora (Carduales). Vol. 33, Part 1. New York: New York Botanical Garden, 1922.
17. Small, W. S., and Small, G. M.: Botanical survey of Southern California. Ann. Allergy, 4:352, 1946.
18. Smith, H. D.; Goodhill, V., and Webb, M. E.: Nasal allergy: The otolaryngologists' problem. Calif. & West. Med., 58:275, 1943.
19. Stealy, C. L.: The pollen content of the air of San Diego, California. J. Lab. and Clin. Med., 22:273, 1936.
20. Van Rensselaer, M.: Trees of Santa Barbara. Joint publication of the Santa Barbara Botanic Gardens and the City of Santa Barbara Board of Park Commissioners, Santa Barbara, Calif., 1940.
21. Watson, S. H., and Kibler, C. S.: Etiology of hay fever in Arizona and the Southwest. J.A.M.A., 78:719, 1922.
22. Wodehouse, R. P.: The ragweeds. Internat. Corresp. Club of Allergy, 5:62, 1942.

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Progress in Allergy

REACTIONS TO PENICILLIN

A Review of the Literature, 1943-1948

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This review was written with the hope that it would be considered as a subtraction rather than an addition to the literature on the subject of penicillin sensitivity. It is based on 308 (of nobody knows how many more!) papers published on this topic from March, 1943 to October, 1948, and an additional fifty-two papers, in which sensitivity is mentioned but neither defined nor described. It does not pretend to be complete, since it is still difficult to acquire papers published abroad during the years of the war and known by reference alone to be concerned with penicillin sensitivity.

In cases in which identical, or almost identical, syndromes were reported by a number of different workers, the earliest ascertainable published report was taken for review purposes. No slight was intended to those others, who, for reasons of space alone in both text and bibliography, had to be completely omitted.

It was not planned that all papers on all phases of the subject be mentioned, but only that the welter of unrelated and separately published more important papers concerned with the phenomenon of penicillin sensitivity be brought together in one place, in so far as an orderly arrangement of the subject permitted. Since many of the workers, and especially those earliest in the field, did not, and perhaps could not, differentiate between toxicity and sensitivity, and no exact classification is as yet available, all untoward sequelae to penicillin treatment are loosely, but purposely, termed reactions as noted in the title of the present review.

Although the Floreys'[41] paper in 1943 mentioned no evidence of sensitivity in 187 patients treated with penicillin, it quickly became apparent (August, 1943) that untoward reactions occurred:—Keefer and his colleagues[62] reported that of 500 cases, sixty-nine demonstrated reactions as fever in five; chills and fever in twelve; thrombophlebitis at injection site in nineteen; urticaria in fourteen; site-of-injection tenderness in five; headache and facial flushing in ten; testicular tingling in two; and muscular pain in two, due perhaps, at least in part, to impurities in the treatment material. In the next paper published, Lyons[75] reported urticaria as the commonest single complication as occurring in 5.7 per cent of 209 surgical (U.S. Army) cases. The author was able to classify the patients into two broad groups: those who had reacted to a particular batch of penicillin with chills, headache, facial flushing, muscular cramps, nausea, vomiting and eosinophilia and those who reacted to any type of penicillin with fever, urticaria and transient azotemia.

By 1946, Duemling[32] was able to summarize the results of therapy in 17,879 Naval patients treated with penicillin for sixty-five clinical conditions. Of these, 892 presented latent, early and neurosyphilis. Of the total group, 10 per cent are listed as having suffered Herxheimer reactions, urticaria, pruritus and fever.

In 1948, Thomas and his colleagues[126] were able to list the reactions in order of decreasing frequency as seen in 10,000 syphilitic patients. Urticaria, which was most common, occurred seven to twelve days after the beginning of treatment in approximately 2.5 per cent of the cases and lasted four to five days, irrespective of the continuance or discontinuance of penicillin therapy. Of 804 patients treated for eight days with penicillin oil-beeswax, two developed angioneurotic edema on the seventh day, but in the majority of cases the penicillin therapy could be continued for eighteen to nineteen days. In three cases, severe urticaria and angioneurotic edema necessitating discontinuation of treatment occurred on the eighth or ninth day, but treatment was resumed ten days later without recurrences. Exacerbation of secondary syphilitic lesions took place six to ten days after treatment started and resembled a relapse excepting that dark field examinations were negative. Erythematous, or papular, eruptions were seen in twenty-five patients within the first forty-eight hours after treatment was initiated and lasted one to three days, all cases continuing their penicillin therapy. Localized dermatitis was seen in very few patients and developed three to four days after treatment was started. A bullous dermatitis

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occurred in two patients, seven to ten days after treatment was initiated and it was necessary to discontinue treatment in one patient, but it was possible to resume treatment after ten days without untoward reactions. The same patient had three recurrences with generalized urticarial eruptions and bullae two months following his discharge from the hospital.

In the series by Cormia *et al*[23] reactions were seen in 0.5 per cent of 2,000 soldiers given prolonged penicillin therapy; these included urticaria, complicated by angioneurotic edema, shock and convulsions or psychotic depression, a syndrome resembling serum sickness, acute syncope with transient miliaria-like eruptions, erythematovesicular eruptions, dermatophytid-like eruptions, erythema nodosum, and epididymitis. In this group of patients, intradermal tests with three brands of penicillin showed that reactions occurred in 84 per cent to one brand and 65 per cent and 23 per cent respectively to the other two. Some patients with severe penicillin sensitivity gave negative tests and some positive reactions occurred in the 116 control subjects. Crystalline penicillin also caused skin reactions.

In the series of 124 male patients studied by Kolodny and Denhoff,[69] 16 per cent showed immediate reactions and 7 per cent delayed reactions, both occurring together in some individuals. The immediate reactions affected 25 per cent of the dermatological but only 6 per cent of the general medical and neurosyphilitic group. Of twenty-one patients with skin diseases, all showed exacerbations of the existing lesions. In some cases, it was associated with a generalized rash, periorbital or labial edema, gastrointestinal symptoms and an "id" reaction. The greater number of reactions appeared within twenty-four, and subsided within ninety-six hours. The incidence of delayed reactions was approximately the same in both the dermatological and the other groups, the symptoms beginning in all but one case in seven to fourteen days and subsiding in four to five; all the patients showing generalized urticaria with pruritus, but some presenting, in addition, swelling of the joints, facial edema, moderate lymphadenopathy, generalized arthralgia, myalgia and malaise. In twelve patients, reactions were produced consistently only if a week or more had elapsed between courses of treatment, suggesting an anergic state of several days' duration. Skin tests done with solutions of 1000 or 2000 U/c.c. (0.1 c.c.) produced consistent reactions, eleven of fifteen reactors, however, giving positive responses to trychophytin skin tests, whereas only two of fourteen non-reactors were positive to penicillin. The conjunctival tests with penicillin were uniformly negative for this group.

In a series of 618 patients studied by Hopkins and Lawrence,[57] seventy were given penicillin by oral and/or intramuscular administration, 492 locally and fifty-six both locally and systemically. Reactions occurred in sixty-five (11 per cent): in one as a generalized urticaria, in three others during an attempt at desensitization and in seven more during tests. Three patients experienced severe pruritus after intramuscular injection, but in only one case was this sufficient to require hospitalization. In eight patients there was a disseminated erythematous or vesicular eruption and in fifty-six a localized dermatitis seen most frequently in those with a pre-existent eczematous dermatitis. Herxheimer reactions were seen in three and local gluteal reactions in two. Tests demonstrated that a sensitization occurred in 13 per cent of the cases treated with ointment; and in 21 per cent of the patients presenting eczematoid lesions. Patch tests were done with penicillin ointment (100,000 U/gm.) intradermal tests with penicillin saline solutions (10,000 U/c.c.), and passive transfer tests were done with the patient's serum and saline solutions (100,000 U/c.c.).

Of nineteen patients who gave positive intradermal reactions to 1,000 units of commercial penicillin, thirteen were positive to the same amount of crystalline penicillin G. Of ninety patients tested, twenty-three gave positive reactions to 100,000 units of penicillin injected intramuscularly, responding with urticaria, erythema and intense generalized pruritus and dermatitis. Of 405 patients given intradermal and patch tests, fifty were positive and 335 negative to both tests, whereas six were positive to patch tests only, and fourteen to intradermal tests only. The authors conclude that sensitization sufficient to prohibit future penicillin therapy would probably occur in less than 1 per cent of the patients treated. They also state that the response to skin tests may vary from week to week and, if possible, may actually become negative.

The reactions to penicillin appear also to depend upon the method of administration. Kern[65] in his case report described a thirty-eight-year-old woman, for whom oral penicillin was prescribed in 10 drops of the 100,000 U/5 c.c. saline solution placed on the tongue every two hours. By the second day, the patient had complained of burning and stinging and presented a sore tongue and throat with tender gums. There was infection of the soft and hard palates, the oral pharynx, the tongue and the gums, with fissuring of the tongue. Symptoms disappeared after three days.

In a similar report, Goldman[47] described a female patient of sixty-one with a recurrent aphthous stomatitis of 15 years' duration. Calcium penicillin ointment was applied three to four times daily with rapid improvement, excepting for one large linear ulcer below the gum. Application of the ointment to this lesion was difficult and a mouth wash of 500 U (sodium penicillin)/c.c. in saline was substituted. Within two days the patient presented a vesicular cheilitis with considerable edema. Patch tests with calcium penicillin ointment were negative, but a positive reaction was seen to the sodium penicillin solution used, although three other brands of sodium penicillin produced no reaction. Application of the reacting solution to the lips produced an edema within twenty-four hours, demonstrating a specific sensitivity to a saline solution of a specific brand of sodium penicillin.

The specificity of the reaction is demonstrated by Wright and Rule[142] who reported severe reactions in 16 per cent of thirty-eight patients treated with penicillin calcium lozenges. The patients demonstrated sore throats, extreme dryness and a burning sensation in the mouth and lips, impaired taste, sensitivity to hot foods and drinks and salty and spiced foods. In three patients a stomatitis developed and persisted for one or two weeks, being followed by a transient exfoliative type of lesion. The discomfort increased for one to two days following discontinuance of therapy and then gradually decreased. The mild glossitis and a sense of dryness persisted in some patients for several weeks. Lozenges of penicillin sodium caused reactions in 9 per cent of 151 patients, proving sensitivity present to both types of penicillin. In the report of the Permanente Foundation[98] seventeen instances of glossitis and stomatitis due to penicillin lozenges were listed, the incidence of reactions with calcium penicillin being given as 18 per cent. The lozenge ingredients were calcium penicillin, powdered sugar and calcium stearate. The binding agent, if any, is not given.

In Kleinfeld's[66] report of six patients given oral and mucous membrane topical applications there was acute rhinitis, stomatitis and glossitis following instillation of penicillin nose drops and oral pastilles in one patient whose glossitis was aggravated after administration of the nebulized penicillin solution. Two additional patients developed lesions of the mouth following the oral penicillin and one a dermatitis of the nares after application of penicillin ointment. In two patients there were abdominal cramps and distention following the ingestion of three enteric-coated tablets and tablets buffered with sodium citrate, respectively, each containing 250,000 units of penicillin. All cleared when the penicillin was discontinued.

Early in 1946 there was correspondence in the British medical journals concerning local oral penicillin reactions. Bedford[5] described melanoglossia (black tongue) in two patients using penicillin lozenges or penicillin throat sprays. The condition occurred on the second post-treatment day in one patient, whose tongue presented a black velvety coat which disappeared on the eleventh day, the tongue becoming normal seven days later. In a second patient, a black tongue developed on the second and became normal on the sixteenth post-treatment day. The author suggested that the "mycotic black tongue may have resulted from an alteration of the normal biological balance of the mouth by the penicillin." Ellinger and Shattock[35] called attention to two of their patients with black tongue following the oral administration of both sulfadiazine and penicillin. The patients treated with penicillin showed, in addition, symptoms of nicotinamide deficiency with skin changes, abdominal pain and sensory disturbance. The level of nicotinamide in the urine indicated deficiency and the symptoms were reproduced by a second and third course of oral penicillin. The patients' symptoms were relieved rapidly by the administration of 100 mg. of nicotinic acid. Thompson[127] noted soon that irritation did not occur in thirty patients given troches with a gelatin base. Further correspondence by MacGregor[78] and by Kerfoot[64] suggested discoloration as due to the base, since the former reported on 1,000 patients treated with gelatin pastilles with only occasional tongue discoloration and no stomatitis. The latter showed that no instances of stomatitis occurred in the patients using the lozenges made with the sucrose base prepared and dried by compression. That these factors are not the complete story is seen by the letter from Mutch[91] who again reports the occurrence of black tongue following oral inhalation and nebulized aqueous solutions of high potency yellow penicillin in a patient taking 50 mg. of nicotinic acid daily. Mutch concludes that the reaction is not due to avitaminosis caused by penicillin inhibition of the nicotinic acid producing bacteria of the gut, but to a local reaction of penicillin itself. Dr. Harold A. Abramson and the present author were able to show that glycerite of hydrogen peroxide in the 1:3 or 1:4 dilution of the 2.5 per cent solution completely cleared this condition.

Penicillin by mouth does, however, cause local reactions as seen by the report of Marcovicci[81] who described six cases, the mildest being an aphthous stomatitis.

In the remaining patients there was a parasitic stomatitis (thrush) which developed during the course of penicillin therapy for infectious mononucleosis; two cases of virus pneumonia and one of streptococcus sore throat. In Brown's case report[12] the patient presented a glossodynia and exfoliation of the filaments of the filiform papillae of the tongue which appeared on the second day following the use of 10,000 U/c.c. penicillin solution as a throat swab and gargle, the papillae of the tongue becoming yellowish brown and felt lifeless. On the third and fourth days the tongue was tender, red and swollen and the filaments easily rubbed off. The tongue became normal in appearance three to four days following treatment with hot saline gargles and the filaments regenerated in two to three weeks.

Cook[20] subsequently reported on twenty-eight patients in four of whom oral penicillin preparations caused stomatitis and glossitis, occurring in one patient 1½ days after using penicillin troches. By the fourth day there were great blisters on the tongue, the soreness disappearing in about a week and the blisters persisting for about a month. A patch test with a portion of one of the troches elicited a wheal and flare in forty-eight hours. Segal and Ryder[110] had previously reported that of the sodium and calcium salts used for inhalation, the latter was the less irritating, although in some patients edema of the lips or oral mucosa and generalized urticaria appeared, the former being controlled by changing the brand of penicillin and the latter by oral administration of Benadryl. Irritation of the tongue and oropharynx was minimized by changing to other lots of penicillin. The sore tongue and oral stomatitis was treated by saline rinses, by dental hygiene and by frequent sips of water during the treatment period.

That the reaction may not be necessarily local is shown by Wheatley's report[139] of a patient in whom a a chickenpox-like rash appeared on the face and chest 20 minutes after the use of a penicillin lozenge, the rash being accompanied by a hot, tingling sensation of the skin and fading in 20 minutes. On the other hand, in the report by Oberst and Murray[93] a severe dermatitis occurred in one of the authors after a large oral dose of penicillin had been taken while he was serving as a subject for the urinary excretion and blood-level studies being done. The patient had previously suffered a reaction following the intravenous administration of 50,000 U. of penicillin, the dermatitis appearing within an hour and being followed in several hours by reddening of the face and itching of the scalp and toes, with areas of erythema over the chest and swelling and blisters around the toes. Subsequently, the same dose was given orally on about 10 occasions, without producing a reaction, but when a dose of 500,000 U. was given by mouth a severe dermatitis occurred, followed in about two hours by itchiness and swelling and blisters of the toes and swelling and reddening of the eyes. There was no previous history of eczema or allergic reactions and the penicillin used was suspended in oil and beeswax enclosed in a gelatin capsule. Since the oral dose, which produced the reaction, was 10 times the intravenous dose, it appears that the penicillin concentration of the blood and tissues was probably about the same in both instances.

In an individual case report, Scott[109] described the occurrence of edematous lips and large urticarial wheals on the abdomen, thighs and upper arms of a four-and-one-half-year-old boy who was sucking penicillin lozenges for the treatment of an enlarged and discharging tonsil. A positive reaction was obtained to a patch test with penicillin ointment (500 U/Gm). The patient's father developed hydroarthrosis of the joints of the knees and fingers while using penicillin lozenges, the joints becoming normal twenty-four hours after the penicillin was discontinued. He also presented a postive skin test.

During the first years in which penicillin was used, it was considered that prolonged contact caused the local reactions. Pyle and Rattner[102] reported early in 1944 that a medical officer in charge of preparing the penicillin solutions, as well as administering the drug to patients, presented an eruption which began as a mild marginal blepharitis and conjunctivitis which spread to the bridge of the nose and far into the central oval of the face, resembling an acute dermatitis due to contact with an irritant. Within a few weeks eczematous lesions appeared on the hands and penis, the eruption completely disappearing in two weeks following his cessation of handling penicillin. In this patient, a patch test to penicillin elicited a strongly positive reaction, additional patch tests indicating that it was the penicillin, not the medium in which it was cultivated, which was responsible for the contact dermatitis. Silvers[115] reported on a chemist who worked for one year with penicillin before developing an itching rash of the eyelids and penis. The patient gave a positive patch test to the yellow amorphous form of penicillin sodium, but a negative test to the pure crystalline sodium penicillin. The rash disappeared entirely when direct contact with penicillin was avoided.

Binkley and Brockmole[8] treated two physicians who were engaged in administering

penicillin to hospital patients, their dermatitis developing within a few weeks after the first use of the drug. Patch tests with a solution of penicillin sodium containing 5,000 U/c.c. was strongly positive in one, whose eruption covered the forehead and lower arms. The patch tests were negative in the second, although an intramuscular injection of 60,000 U/ caused pruritus and an eruption of the hands and feet. The dermatitis of both men disappeared when contact with the drug was avoided or minimized.

Barker's[4] patient was a medical officer in charge of a penicillin laboratory of a large hospital. He had handled penicillin under laboratory conditions for seven months with no untoward effects, but one day while dispensing penicillin solutions, spilled some on his hands. The next day there was a pruritus of the face, which disappeared while he was on leave. As soon as he returned, however, to dispensing the penicillin solutions, an acute dermatitis of the face and neck developed with an edema of the upper and lower eyelids and a tightness of the skin of the face, followed by a vesiculation and serous exudate of the chin. Patch tests made with penicillin solutions (20,000 U/c.c.) produced an eczematous reaction in twelve hours, but the same solutions, after autoclaving, were negative. The authors suggest that in this case the irritant in the penicillin solutions might be volatile, due to the selection of the face as the first site of attack and the disappearance of the effect with autoclaved solutions.

The great variation in the type of contact reaction was demonstrated by the patients reported by Catherine MacInnis[79] whose patient, a nurse, had reacted with generalized urticaria following the therapeutic administration of penicillin. Two months later a generalized itching and wheals on the legs occurred forty-eight hours after handling the drug and entering a room where penicillin was being prepared produced a nasal congestion. A second patient, who had never received penicillin therapeutically, but had been handling the drug intermittently over a period of several months, developed an itching, redness, whealing and a fine papular rash of the face and arms associated with photophobia and nasal congestion when contact with the drug became more frequent.

The amount of contact dermatitis due to penicillin was indirectly ascertained from the patients who used an ointment containing the drug. In the cases described by Cohen and Pfaff,[18] 4 per cent of 100 patients presented contact reactions following the use of an unguent containing 50,000 U/oz., in 50 per cent hydrous wool fat and 50 per cent rose water.

The patient may be sensitized at one site and react generally as shown by the report of Michie and Bailie,[86] whose patient had penicillin sodium solution instilled into a wound on September twenty-four and undiluted penicillin powder applied to a sinus on October 2, the wound having completely epithelialized by October 10, when two drops of penicillin solution (100,000 U/c.c.) were instilled into the ears for a mild chronic bilateral otitis externa, both the ears and the almost-healed leg wound beginning to weep copiously. A patch test made on the arm with the penicillin solution used produced a weeping eczema similar to the affected area, the eczematous weeping eruption spreading to the face.

According to Morginson,[88] who treated 102 dermatological conditions in eighty-five patients, topical applications for longer than three to four days frequently induces contact dermatitis. In some cases, however, as seen in the patient described by Markson,[82] penicillin ointment applied in the case of mild conjunctivitis caused an edema of the eyelids by the next morning and when the ointment was re-applied after discontinuance for one day the edema became more pronounced and was associated with an erythematovesicular dermatitis appearing on the eyelids and other parts of the face. The patient had previously been treated with sulfathiazole ointment, for which the patch test was negative, although a test to the penicillin ointment produced an erythematovesicular eruption. The ointment base was the same for both preparations.

The patient described by Bedford[6] was evidently sensitized by mouth and responded by contact. Having been successfully treated for a nasopharyngitis and tracheitis with penicillin pastilles (300 U) and a throat spray (250 U/c.c.) he responded one week later when penicillin solution (250 U/c.c.) was instilled hourly for a mild conjunctivitis with an itching vesiculopapular rash which appeared on the lower lids where the excess solution had been wiped away. The rash subsided in 8 days. Of interest is the fact that the patch test made on the arm with the original solution, which had been allowed to become inert, as well as with a fresh penicillin solution, gave negative results. A fresh solution, however, gave a positive reaction when used as a test on the site of the previous lesion.

In some patients such sensitivity may be of more than one type. Benkwith[7] treated a Naval officer for a diffuse palpebral conjunctivitis with penicillin calcium solution,

instilled in the lower conjunctival cul-de-sac hourly for two days. A typical allergic dermatitis appeared on the eyelids, nose and adjacent face. A patch test using the ointment produced a very severe reaction, the base being negative. An intradermal test with the penicillin solution used produced an urticarial wheal, the patient being equally allergic to penicillin from two different manufacturers.

The length of time necessary for the development of sensitization may vary greatly, as seen in the case described by Vickers[130] whose patient had penicillin powder applied to abrasions on the leg at various times from May 22 to July 5, 1945, and was then treated by intramuscular penicillin drip until July 12. At this time a dermatitis appeared at the site of the drip and a penicillin spray was used locally, resulting in an erythema, vesiculation, weeping and crust formation over the inner surface of the leg. Patch tests with the penicillin solutions used were strongly positive in twenty-four hours. The incubation period for this sensitivity was evidently approximately forty days.

Few patients present the variegated sensitivities to intense study and treatment as that described by O'Donovan and Klorfajn.[94] In June, 1944, the patient presented fissures of the left foot treated with penicillin sprays without benefit. In October, 1944, an abscess of the left jaw was treated for three days with penicillin sprays. Two weeks later a rash developed, both on the left foot and on the face. This subsided, but in December a recurrence of the foot condition was treated with a penicillin spray, resulting in a rash at the site of the spray and on the face. The patient gave positive patch tests, intradermal tests and spray tests with the penicillin solution. An intramuscular injection of 15,000 units of penicillin produced severe anaphylactic shock, followed in six hours by swelling, reddening and oozing of the face, and redness and weeping of the right eye. Exposure to ultraviolet light, both by sun and lamp, produced erythematous reactions. An attempt to desensitize the patient by the subcutaneous injection of 100 units of penicillin produced a mild shock. Penicillin (15,000 U.) capsules given orally caused swelling of the face, neck, scalp and ears, a leukocyte count [illegible], and complaints of malaise and drowsiness. The oral treatment was continued [illegible] days, following which the patient became negative to patch tests and [illegible] sented the actinic reaction. In this patient, regardless of the means by which [illegible]lin was administered, the skin reactions occurred only at the sites initially [illegible]d demonstrating a purely local sensitivity.

Templeton and his colleagues[125] reviewed the [illegible]ic reactions occurring after the topical application of penicillin solutions and ointments, after the injections and after oral administration. They recommended that topical use be avoided. Their studies show that the application of a 1,000-unit penicillin solution to the skin of seven subjects at the site of a previous injection of the serum of patients who reacted to penicillin caused positive reactions.

The medium in which the penicillin is dissolved must, however, not be completely ignored, since in Meara's report[83] patch testing of three patients with skin sensitivity to penicillin revealed that the penicillin as such was not responsible for the eruptions. The incorporation of the penicillin in a non-offensive cream base was necessary before sensitization took place in one patient. In two other patients, an ingredient of the ordinary ointment base was the responsible agent.

The exquisite sensitivity which may develop with contact to penicillin is shown in the report by Prince,[101] whose patient showed an eczematous reaction to contact with penicillin, an injection of 0.02 c.c. of a 1 unit/c.c. strength causing an eczematoid eruption on distant parts of the body, with sneezing as well as local itching from the injections.

Studies to elicit the cause of such cutaneous reactions have been done by Goldman and his colleagues.[48] In 350 cases of various cutaneous conditions treated with topical penicillin, sixteen responded with an eczematous reaction. All but two gave positive patch tests, the patients being tested with impure commercial penicillin, crystalline penicillin and penicillin inatcive (according to assay), or inactivated by penicillinase. Of thirty-two men with acute pyogenic infections, nine developed contact dermatitis following the use of the ointment, although only three of eight women with similar lesions reacted in this way. Patch tests on 216 control patients, with an ointment containing 18,000 U/cm. of commercial calcium penicillin produced no reactions during an observation period up to seven days. When retested two weeks later, however, thirty-five of the patients reacted positively. It was determined that penicillin ointment in the concentration of 18,000 U/gm. was not a primary irritant. In this series, seven cases of patients with urticaria following the parenteral use of penicillin gave negative skin and passive transfer tests.

Friedlaender *et al*[43] carefully studied four of five patients presenting contact

dermatitis resulting from the handling of penicillin. Patch tests were made with all of the substances entering into the manufacture of penicillin by the submerged broth method. Tests were also done intradermally with mould extracts. Three patients gave positive reactions to crystalline penicillin as well as to various intermediate products. One patient gave a positive reaction to Penicillium mould; one patient reacted strongly to chloroform extract, and one gave a mild reaction to the mould mycelium. None reacted to the corn steep liquor. Contact periods of nine to eighteen months were required before sensitivity developed.

Since urticaria seems to be the most common reaction, its varieties merit detailed description. Hives may appear in a period as short as twenty-five minutes and up to and beyond the thirty-fifth post-treatment day. Strickland's report[121] concerns a twenty-two-year-old male, who ten weeks previously had received successful penicillin treatment for a gonococcal urethritis and who, when given an intramuscular injection of 20,000 units of penicillin for cellulitis in the perineal region, developed a generalized urticaria with a bilateral periorbital edema associated with pain and effusion of the right wrist joint and edema of the pharynx and larynx characterized by hoarseness and difficulty in swallowing within twenty-five minutes after the initial injection of the second course of treatment. Epinephrine (0.5 c.c. 1:1000 solution) was administered and within twenty-four hours the condition completely cleared. In Krauel's case[70] 10,000 units of penicillin sodium caused urticarial pruritus, redness and intense itching of the palms of the hands in a seaman, who two days later presented pain in the right knee and the left ankle with a temperature rise each evening. This patient had a history of hay fever while cutting grain infested with the rust fungus and of sensitivity to house dust.

In the case described by O'Donovan and Klorfajn,[94] the local reaction occurred six hours after injection. The patient's initial contact had caused no difficulties, while four months later, three days of penicillin treatment was given without untoward reaction. Two weeks later the application of penicillin by spray caused an immediate response with edema of the upper lip, nose and eyebrows and a maculopapular rash of the cheeks and neck. An intramuscular injection of 15,000 units of penicillin caused anaphylactic shock within fifteen minutes, with a local reaction occurring on the face six hours after injection. Three weeks later exposure to ultraviolet light caused a repetition of the reaction in the patient who by now showed positive patch, intradermal, and intramuscular sensitivities. Canizares[16] had the year before questioned whether penicillin was a photosensitizing agent, since his patient, who was treated with 10,000 U. penicillin every three hours to total 50,000 units, had (when taking a sun bath the following day) developed a severe sunburn, which subsided. A morbilliform eruption appeared on the previously sunburned areas four days after the penicillin treatment and faded after two days.

Cuthbert's case[26] developed hives one day after the cessation of penicillin therapy during the course of which the patient received 6,400,000 units in sixteen days following Caesarean section. The hives lasted 6 days and were accompanied by severe pruritus but not by fever or tachycardia. In the case studied by Flinn *et al*[40] the patient had six months previously received 4,000,000 units of penicillin intramuscularly. She developed a pruritus and a severe urticaria with a rise in temperature after being given 200,000 U. of Brand B penicillin intravenously daily for nine days and 30,000 at three-hour intervals intramuscularly for another two days for treatment of a respiratory tract infection. The severe urticaria and pruritus subsided seventy-two hours after penicillin withdrawal. In this patient, intradermal tests showed sensitivity to Brands A, B, and C but not to D. The treatment was continued with this latter brand with no reactions. Six weeks later the patient had lost her sensitivity to Brand B, which could be used for treatment. The authors believe that the incidence of urticaria in penicillin-treated patients is approximately 3 per cent.

In four patients studied by Macev and Hays,[76] the allergic manifestations appeared two to five days after penicillin was discontinued, the patients presenting an increase in pulse rate and elevation in temperature, a swelling of the face and hands, with elevated erythematous lesions accompanied by intense itching. Symptomatic relief was achieved with the administration of 10 per cent calcium gluconate or 50 per cent dextrose given intravenously. Each of the two cases described by Watson[137] is interesting; the first because the patient responded by drowsiness and indigestion as well as urticaria persisting for seven days after receiving penicillin 250,000 U. in distilled water b.i.d. for three days. The symptoms persisted for seven days in spite of the administration of Benadryl and epinephrine. The second patient, previously having been successfully treated for a carbuncle with 150,000 U. of penicillin in distilled water every three hours for five days received gluteal injections of 250,000 U. of penicillin beeswax in oil b.i.d. twice daily for three days for a second carbuncle. Eight days after the first injection, itching and a wheal at the site of an

old bee sting developed with urticaria and swelling of the sites of injection persisting for one week. Exacerbation of symptoms occurred when the patient ate honey. Benadryl controlled the allergic reaction but only to a slight extent.

The patient described by Price[100] was given intramuscular penicillin, 20,000 U., three hourly and on the fifth day of treatment developed a punctate purpuric eruption on the arms, abdomen, chest and back. On the same day, a small urticarial wheal appeared on the left upper arm and two days later there was a severe giant urticaria with a rise in temperature, a periarticular arthralgia and increase in white count to 17,700 with the appearance of pus cells and casts in the urine. The reaction responded to epinephrine therapy. Scratch and patch tests with penicillin solutions were negative, although an intracutaneous test of "human serum containing penicillin" produced a positive reaction.

In Tripoli's case report[128] one patient developed urticaria and fever on the fourth day and the second a temperature of 101°-103° F. on the seventh day. Wilensky's[141] patient, given penicillin 30,000 U. four hourly for five days presented an elevated temperature of 104° F. with the appearance of a scarlatiniform rash covering the trunk, abdomen and thighs. By the sixth day the condition had become more severe, spreading to the thorax, neck, face and arms, the patient dying of fatal delayed anaphylactic shock on the eighth day.

Although in a number of individuals the onset of urticaria is seen in those who are taking a second course of penicillin therapy, some patients develop a sensitivity after the third course, as noted in the report by Dolan,[30] whose patient had received penicillin intramuscularly two months and one year previously. He developed a severe angioneurotic edema and muscle pain six days after taking 200,000 U. of penicillin orally for a head cold and a mild otitis media. The urticarial reaction was associated with itching. The muscular pain was controlled for six days by Benadryl but still present in some degree one month after cessation of treatment.

That both an acute early and delayed reaction to penicillin may occur is seen by the report of Burt and Caplan,[13] whose patient was given penicillin oil and beeswax for the treatment of a furuncle. Six hours following the initial injection which was made in the midportion of the left thigh the area down to the knee was sensitive and three hours later motion was not possible. There was a concomitant fever, headache and malaise. The following day the area appeared normal but there was a serous exudate of the knee joint and weight-bearing was painful. Since the furuncle was still firmly inflamed, crystalline sodium penicillin G in aqueous solution was given intramuscularly in the right buttock, as two injections of 100,000 U. on successive days. The symptoms of the previous reactions subsided and the furuncle healed, but nine days after the initial injection there was a pruritic urticaria of the area and the exudate from the knee joint reappeared, followed two days later by swelling of the left thigh, the leg and the ankle, the skin being thickened and doughy. The pruritus was controlled by PBZ, the other symptoms subsiding in four days. The patient had a history of ragweed pollen sensitivity and the authors suggest that the reaction may have been due to ragweed pollen and the beeswax or to an early serum-sickness-like reaction to penicillin.

A severe urticaria occurred in 11 days after intramuscularly administered penicillin was reported by Walley[136] whose patient, a thirty-two-year-old Army officer, received five injections of sodium penicillin twelve hourly for the treatment of an infected hematoma. In eleven days after treatment was discontinued, the patient presented a widespread urticaria with intense pruritus, associated with fever, anorexia, indigestion and vomiting. The patient was unable to tolerate Benadryl. The symptoms subsided slowly during the following eight days.

Urticaria occurring in a physician thirteen days after the cessation of penicillin therapy is described by Strazza,[120] whose patient was given 20,000 U. intramuscularly, three hourly, for a total of 500,000 U., with itching of the site of injection and flushing of the face during therapy. The patient returned thirteen days later with an urticaria and pruritus so severe that he required 6 c.c. of epinephrine (1:1000), the urticaria covering the buttocks, back, face, hands, feet and uvula, and increasing within thirty hours to so great a degree that the patient had difficulty in swallowing due to edema of the pharynx and uvula. Within forty hours there was stiffness of the neck, the symptoms subsiding in three days. A scratch test to the penicillin used was negative.

In Truitt's[129] patient a painful arthritis, angioneurotic edema and generalized urticaria developed fourteen days after treatment with penicillin had stopped. In this case, patch, intradermal and passive transfer tests were all positive, the first two being still positive nine months after the reaction. A patch test remained positive four months after the reaction but passive transfer tests were negative.

The interval between courses of treatment may be important as shown in the case

described by Criep[25] whose patient, a twenty-three-year-old male, had received 200,000 U. of penicillin daily for fourteen days. On resumption of therapy after a ten-day interval, the first injection caused a severe generalized urticaria, which persisted for six days, during which time 120,000 U. were nevertheless administered daily. Although direct skin tests with penicillium extract were negative and the presence of anaphylactic antibodies could not be demonstrated in the patient's serum, direct intradermal skin tests, passive transfer tests and precipitin tests were positive to the penicillin drug solution used.

Shawyer's[114] case report is concerned with a thirty-four-year-old physician who received 7,500,000 U. of penicillin five days for a bone abscess. His condition improved until seventeen days after discontinuance of penicillin, when a general simple urticaria, uncontrolled by Benadryl, appeared. By the second day the patient developed an angioneurotic edema and by the fifth, a generalized swelling of the joints with intermittent edema of the fauces, glottis and tongue, bronchial asthma and paroxysmal rhinorrhea. The urticaria and the joint lesions subsided following a course of synthetic Vitamin K. The patient did not respond to Benadryl, epinephrine or Anthisan. Vitamin K, however, in 20 mg. doses, caused immediate disappearance of the pruritus.

Severe urticaria occurring twenty-one days after the termination of a four-day course of penicillin treatment is reported by Mandel et al,[80] whose patient, an eight-and-one-half-year-old child, was given penicillin because of a secondary rise in temperature and earache during the course of an acute upper respiratory tract infection, the dose being 0.5 c.c. of calcium penicillin in beeswax and peanut oil by intragluteal injection once daily for three days. The patient also received 100,000 U. orally for one day. Swelling, induration and erythema developed at the sites of injection, being most prominent on the fifth and seventh days after discontinuance of therapy. These subsided with local treatment, but twenty-one days later the patient presented a swelling of the cervical lymph nodes and fever (102.5° F. rectally) followed in twenty-four hours by urticaria, angioneurotic edema, anorexia, vomiting and general malaise. The symptoms subsided in seven days, but fourteen days later (forty-four days after discontinuance of penicillin) giant urticaria and angioneurotic edema developed, subsiding in four days, the residual exfoliation and pruritus persisting for about one month. Scratch tests with calcium penicillin-beeswax-peanut oil, its constituents, the amorphous sodium penicillin and crystalline potassium penicillin, as well as trychophytin tests, were all negative, excepting for a moderate erythema at the scratch test sites of penicilin in oil-beeswax.

Hinman *et al*[55] described delayed reactions in seven patients, occurring two to twenty-eight days after cessation of therapy, the symptoms being giant urticaria, intense pruritus, scarlatiniform eruptions, severe arthralgia, hydroarthrosis, ecchymoses and subcutaneous nodules as well as systemic manifestations including fever, prostration, gastrointestinal symptoms, severe headache, mild leukocytosis and albuminaria. The incapacitation lasted about two weeks. In their patients the reactions were not related to the size of the dose, the duration of therapy, the route of administration, previous penicillin therapy or a history of allergic conditions, such as asthma, hay fever, or urticaria.

A generalized urticaria and angioneurotic edema appeared five weeks after parenteral administration of 100,000 U. for five days in a patient described by Scott, Murray and Turnbull.[109]

Urticaria may also be due to concomitant treatment as seen in the patient studied by Grolnick and Loewe.[51] Receiving combined treatment with penicillin and heparin daily, he developed a reaction comprising chills and fever on the sixteenth day when a total of 1,600 mg. of heparin had been given. The therapy was resumed 12 days later and continued for twenty-eight days. The subcutaneous injection of heparin concomitant with the intramuscular injection of penicillin for three alternate days after a two-day rest resulted in another reaction. Further attempts to administer the drugs produced erythema and urticaria in addition to the chills and fever. Reagins were present to heparin, beef serum and beef lung. The heparin rather than the penicillin was considered the cause of the reaction.

Although urticaria may be the sole reaction to penicillin, it may occasionally be associated with other signs and symptoms of serum sickness. Sullens[122] presents a case history which illustrates the difficulty in determining the causative agent of the allergic reaction to the therapeutic use of the antibiotic agent. A white seaman, who complained of a purulent urethral discharge and dysuria occurring six days after sexual exposure, was given sulfathiazole for three days with no improvement. He was then given 100,000 U. of calcium penicillin in five intramuscular injections at three-hour intervals, which resulted in freedom from symptoms within one day and a negative prostatic smear two days later. The patient returned in three weeks with

the recurrence of his urethral discharge and a second course of 100,000 U. was given, the patient being well for six days, at which time he developed large urticarial welts on the abdomen, back, hips, with arthralgia of the wrists and ankles and an edema of the hands and feet associated with a generalized lymphadenopathy, headache and a temperature of 99°F. The condition remained unchanged for three days, the urticaria spreading, however, to the extremities, face and scalp, the wheals measuring 2 x 15 cm. Although the symptoms began to diminish after the third day some urticarial areas persisted for six days. Epinephrine 1:1000 by injection relieved the itching and resulted in an almost complete disappearance of the hives for about three hours. Ephedrine and Benzedrine orally had little effect. One week after the symptoms had disappeared skin tests with penicillin solution showed no reaction at the sites of injection, but five hours later urticarial wheals appeared on the skin of the upper arm above the site of the skin test, the reaction being limited to the arm on which the tests were made. This reaction disappeared in about three hours and the author feels that it was not determined that the reaction was due to the penicillin or to an impurity in its preparation.

Four of fifty-six patients treated by Haswell and Wilkinson[53] developed serum-sickness-like reactions six to twelve days after their first injection. In all cases, the symptoms included a low-grade fever with malaise, a generalized urticaria and a patchy erythema. In some instances there was adenopathy, a transient edema of the eyes, mouth, and limbs and an anorexia. Although the penicillin differed in brand, cutaneous tests by patch, scratch, and intradermal techniques in all cases were negative.

Gordon[49] reports on three patients who respectively reacted with urticaria on the second, fifth and seventh days after the discontinuance of penicillin therapy, in all cases responding as well with pain and swelling of the joints, local warmth and painful motion, slight edema and tachycardia. In two cases the eyelids were swollen and in all three the last phase of the reaction was an exfoliative dermatitis of the palms of the hands. Epinephrine by injection controlled the hives in three, five and three days, respectively, with the arthralgia disappearing on the fifth and seventh days in two cases and persisting for ten days in the third. The dermatitis was the last reaction to disappear. The author believes that the type of reaction can be attributed to impurities in the penicillin and that it is an allergic reaction and should be treated as such, perhaps by desensitization.

Kendig and Toone[63] present three additional cases similar to Gordon's excepting that the patients were all of the same family, their reactions covering a period of six weeks. In none of these was there any exfoliative dermatitis; one patient had presented a mild urticaria several years previously, presumably due to egg, and a second had suffered from a trychophytin infection of moderate severity. The authors state that the course of the reaction may vary from five to fourteen days regardless of the treatment used.

In the five cases reported by Strakosch[119] the symptoms not only included those listed above but also abdominal cramps, and a secondary anemia with an increase in the sedimentation rate and a leukocytosis. The author suggests that in some cases the symptoms may resemble those of acute rheumatic fever and may lead to a false diagnosis. This series is interesting in that three of the patients gave local and constitutional reactions to skin tests with a commercial penicillin solution (50 U/0.01 c.c.). In one case the symptoms occurred four days after termination of a course of 1,200,000 U. of sodium penicillin given for a sore throat, with the urticaria disappearing in three days, the arthralgia in eleven and the lymph node enlargement in twenty-one days. A second course of 700,000 U. intramuscularly seven weeks later caused, however, no ill effects.

In Eisenstadt's[34] two cases, the first had had a five-day course of penicillin therapy a month before the onset of his symptoms which arose eight days after the termination of a course of penicillin therapy given for pneumonia. In this patient, a skin test with a commercial penicillin preparation was negative three weeks later, the symptoms having subsided in six days. In the second patient, the penicillin had been given nine months previously, the symptoms occurring eight days after conclusion of a total of 100,000 U. followed two days later by a single injection of 100,000 U. in beeswax. The symptoms subsided in four days. The intradermal test with the commercial penicillin was positive, with that of the diluent being negative.

Mendell and Prose,[84] who treated more than 5,000 cases at a station hospital on Luzon with penicillin, reported only six cases (0.12 per cent) as being reactions sufficiently severe to require discontinuance of the drug. In four cases the reactions were suggestive of a drug allergy, whereas in two they were delayed and simulated serum sickness. The former cases demonstrated a pruritus, an erythematous rash, and edema and a fever with eosinophilia present in three, the symptoms subsiding within a few

days. In all cases, passive transfer precipitin and conjunctival tests were negative but patch tests were positive in all. The intracutaneous test was positive in two, while in the third it was positive with the brand of penicillin used, but negative with another brand. In the second series of two cases, reactions developed two and seven days respectively after termination of intramuscular penicillin therapy, both patients presenting symptoms of fever, generalized severe giant urticaria, pain and swelling of the joints, with dyspnea and wheezing occurring in one patient and requiring epinephrine for relief. Two hundred control subjects were tested to penicillin by the skin and conjunctival methods and then given 50,000 U. parenterally of the same brand of penicillin. The authors state that the intracutaneous and conjunctival tests were unreliable in predicting severe reactions, although patch tests might prove of value in detecting penicillin sensitivity.

A number of other reports of the same type have since appeared, all being similar in nature, and since they bring forward no new data, it was felt that they ought not to be either abstracted or listed.

Occasionally the reaction may be purely local, following injection as seen in the case described by Lederman,[72] whose patient took nine injections of penicillin in beeswax-peanut oil daily, but with the tenth injection developed a lump at the site and following the eleventh injection, presented red, hard areas around the sites of all of the previous injections. There was no pain, fever, or malaise. The patient was unable to tolerate various brands of penicillin in aqueous solution, once daily, as well as another brand of penicillin-beeswax-peanut oil in doses up to 7,500,000 units. There are no new infiltrations but the lumps from the first series of injections lasted over two months before gradually disappearing.

The patient described by Switzer[124] reacted within one week to the first intramuscular injection of 1 c.c. of penicillin-beeswax-peanut oil, the local reaction being associated with a temperature of 100.2°F. Benadryl caused symptomatic relief, but the reactant area did not involute for almost two months. Since the patient had previously taken penicillin orally, it is suggested that she may have become sensitized to the penicillin, to an impurity or to the beeswax-peanut oil.

Blechmann *et al*[9] reported on two three-week-old twins, who each received twelve injections of penicillin-beeswax-peanut oil and who both presented indurations and tumors which ruptured spontaneously at the sites of injections in the gluteal areas.

Of special interest is the patient described by Call and Gilbert.[14] Four weeks after treatment of a cellulitis of the right hand with oral sulfadiazine and 320,000 U. of penicillin (intragluteally) the patient developed a large number of abscesses at the site of the penicillin injection. Four weeks later the patient was given intragluteal injections of 1,040,000 U. in the treatment of soft tissue wounds of the leg and again developed multiple abscesses of the buttocks with a large furuncle of the right leg four weeks later. He was given intramuscular penicillin for the treatment of these and again in three weeks developed a group of furuncles on the legs with abscesses at the site of the penicillin injections. Once more, intramuscular penicillin was given, to be followed in five weeks by abscesses at the site of injection. Following the use of penicillin for a fracture of the mandible the patient developed a furuncle, and intramuscular penicillin cured this furuncle, but ten days later it was followed by abscesses at the site of injection. The furuncles showed a growth of staphylococcus aureus and the cycle of intramuscular penicillin and abscess formation was reported on two additional occasions. Intramuscular injection of 200,000 U. in sterile water was followed by the appearance of a sterile abscess at the site of injection. The diluent alone produced no reaction. Since the various courses of penicillin the case were given at different hospitals, the authors point out that contamination of penicillin as a factor in the abscess formation was highly unlikely. The conjunctival test was negative.

Since conjunctival tests have frequently been used as a method of proving penicillin sensitivity, the reports regarding eye reactions should be listed at this point. Early in 1946, Satulsky[105] reported on a thirty-one-year-old soldier diagnosed as having a severe chronic ulcerative keratitis of the right eye. Penicillin in a petrolatum lanolin ointment base (1,000 U/Gm.) was instilled into the affected eye and within a few hours the patient demonstrated a severe conjunctivitis with a dermatitis of the eyelid and the adjacent areas of the face. The ointment was discontinued and the symptoms subsided in several days. A patch test with the penicillin ointment and with crystalline penicillin gave no positive reactions, while the constituents of the ointment base were negative in reaction. The subsequent instillation of penicillin solutions (5,000 U/c.c.) produced a recrudescence of the symptoms.

Local sensitivity associated with a generalized sensitivity was reported by Welply[138] who treated himself with penicillin drops (1,000 U/c.c.) for a mild conjunctivitis. The eyelids became red and swollen with irritated margins, the condition clearing when penicillin was discontinued and sulfacetamide instilled. On two subsequent oc-

casions, penicillin therapy produced the same reactions. Of interest is the fact, however, that after an interval of some months when the patient was given local insufflations of penicillin-sulfathiazole powder for the treatment of an old mastoid sinus the eyelids responded with redness and swelling within twenty-four hours, the condition improving when the insufflations were discontinued.

Selinger's[111] patient developed a severe dermatitis of the eyelids five days after he began instilling a penicillin solution (250 U/c.c.) into each eye at two-hour intervals for a conjunctivitis. Schultz,[107] who reported on two of fifty-two patients treated with intraocular instillations of penicillin ointment or a solution containing 500-3,000 U/Gm. (or c.c.), described a dermatitis of the eyelids in which the first disappeared when therapy was halted but flared up into an acute ocular dermatitis with three instillations of penicillin solution two days later, the scaliness persisting for five days. The second patient presented a contact dermatitis of the upper face and eyelids after two drops of the solution had been instilled every two hours for four days, the eruption also clearing within five days. Intracutaneous tests were positive in both patients, with patch tests positive in the second.

Pruritus alone as a side effect of penicillin therapy was described late in 1944 by Freyhon.[42] The patient had received 100,000 U. for ten days for the treatment of a pulmonary abscess. A severe generalized pruritus occurred five days after the administration of the antibiotic had been discontinued and then gradually subsided.

Not only may the patient respond with a pruritus without a rash, but he may also have a rash without pruritus as described by Holden[56]. The patient, a fifty-two-year-old male, with lobar pneumonia, who received 30,000 U. of penicillin every three hours for three days, developed a non-itching, non-papular rash spreading over the body. Passive transfer tests with penicillin produced wheals 2.5 cm. in diameter in a test subject as compared with areas of erythema, 0.6 cm. in diameter obtained with controls. The rash faded within three days and was followed by a five-day period of desquamation after discontinuance of penicillin treatment.

That the rashes may vary in type was seen by the report of Gent and Mackinnon[46] whose patient developed a morbilliform rash after the second injection of 30,000 U. of penicillin given at four-hour intervals for a tonsillitis. Rigor had followed the first injection and the rash followed the second. After discontinuance of penicillin, both abated.

An anaphylactic purpura following intramuscular penicillin therapy was described by Anderson[1], in whose patient a second course of penicillin therapy consisting of 15,000 U. intramuscularly every three hours for a period of nine days caused a purpura associated with transient swelling of the joints and subcutaneous tissue and a toxic nephritis. The patient was treated with epinephrine by injection, by oral glucose and vitamin preparations, the symptoms diminishing in twenty-five days.

The patient treated by Vogel[131] for a pustulosquamous dermatitis with 250,000 U. of penicillin given intramuscularly every three hours developed a severe exfoliative dermatitis after the ninth dose. A second patient studied by the same author developed an edema of the face and a giant urticaria of the body following the topical use of a cream (100,000 U/60 gm. of a cetyl alcohol base) for twenty-four hours. Urticaria, as noted above, has been more often described as following intramuscular injections.

That a rash and urticarial reactions may occur together is suggested by the report of Gottlieb and Frankland,[50] whose patient, aged eleven, was given 5 daily injections intramuscularly of 2 c.c. 125,000 U. penicillin-beeswax-oil and who, on the eighth day of treatment, developed a swelling of the injection site, a slight edema and a generalized rash. Symptoms disappeared spontaneously four days after discontinuance of penicillin therapy.

The exfoliative dermatitis reactions may be extremely severe. Farrington and Tamura[38] reported on a seventy-eight-year-old white man treated with intramuscular penicillin for lobar pneumonia. On the fourth day the patient presented a generalized erythematous maculopapular eruption which, during the next three days, became a generalized diffuse erythematous vesicular eruption covering the entire body and followed by a widespreading exfoliation of the epidermis and loss of the nails, receding over a period of four weeks. The patient responded to intradermal and contact tests with both the urticarial and tuberculin types of reactions. He reacted to different commercial brands of penicillin and to commercial penicillin K, but not to autoclaved material; to crude inactive extracts or penicillinase-inactivated extracts. Patch test with trychophytin, gliotoxin and streptomycin were negative, although an intradermal test with trychophytin was positive.

The patient may be sensitized by contact and react by injection as described by Shaffer.[113] A twenty-seven-year-old male with impetigo was treated with penicillin ointment (1,000 U/c.c.) petrolatum base. On the fourth day of the treatment the

patient developed coalescing vesicular lesions of the left cervical region and the right angle of the mouth, with an erysipiloid lesion appearing in two days on the area to which the ointment had been applied. Intramuscular injection of 30,000 units, three hourly, was instituted with no improvement of the lesions, but with the development of a severe pruritus and a generalized maculopapular eruption progressing within seven days to an exfoliative reaction involving the entire body. The impetigo cleared after treatment with ammoniated mercury. The author cautions against the use of penicillin ointments in the treatment of skin lesions.

The severe degree to which this exfoliative dermatitis may follow either injection or contact with penicillin and the various types of sensitivity which may occur are all seen in a patient described by Derzavis and Beinstein[29] whose patient, a fifty-six-year-old white man, received a single injection of 300,000 units of penicillin-beeswax-peanut oil for the treatment of a traumatic cellulitis of the right finger and a regional epitrochlear lymphadenitis. Six hours following the injection, the patient developed a generalized severe pruritus of the lower extremities followed by an acute erythematous eruption involving the extremities and genitalia, progressing to a hemorrhagic vesiculation during the next three to four days, the vesicles becoming ulcerated and gangrenous. The second type of reaction was shown on the tenth day when the temperature became elevated and a delayed serum-sickness type of reaction appeared. The dermatosis reached its peak between the twentieth and twenty-fifth days and gradually subsided with the healing of all of the lesions during the following month.

Such exfoliative dermatitis types of reaction may be delayed as described by Farrington *et al.*[37] There were no untoward reactions in a patient given 50,000 U. intramuscularly every three hours, using the amorphous commercial material for 5 days, after which there appeared a generalized erythema and twenty-four hours later, a typical erythematous generalized maculopapular dermatitis associated with intense pruritus, the rash being most marked in the axillae, groins, and flexures of the elbows. The patient's original eye condition had shown much improvement and the penicillin therapy was discontinued. At the end of forty-eight hours, the pruritus, erythema and rash had almost entirely receded. The patient was patch tested to 200,000 U. penicillin G on the upper right arm, the reaction site being negative at the end of forty-eight hours. An intradermal test (2.5 U. of crystalline penicillin G/0.1 c.c. of normal saline) produced an immediate erythema and an edema with an accentuation of the original injection wheal. There was a slightly elevated central edema that spread into pseudopodia, appearing within twenty minutes and receding in 1 hour. An accentuation of this reaction was noted in six hours and persisted as a tuberculin type of reaction for forty-eight hours. A control intradermal test with normal saline (0.1 c.c.) was negative. At the end of this time an exacerbation of the keratoconjunctivitis, which did not respond to topical sulfathiazole, suggested that penicillin therapy be resumed. It was used as a topical application (500 U/c.c.) of the amorphous penicillin in normal saline. There was improvement for forty-eight hours, following which an erythema, edema and vesiculation were noted on the periorbital region of the affected eye, the cheek and the adjacent areas of the face. A patch test with this material on the arm was negative, but on the angle of the jaw gave a 2-plus reaction in twenty-four hours. A repeated intradermal test with 200 U. of amorphous commercial penicillin on the right forearm gave no immediate reaction and was negative when seen at the end of forty-eight hours. Thirty-one days later the patient was retested by the intradermal method with 2.5 U. of amorphous penicillin, using the same brand and lot number, and reacted with an immediate reaginogenic type of reaction as well as a later tuberculin type of reaction at the end of forty-eight hours. A repeat patch test with 200 U. of the same amorphous penicillin gave a 2-plus reaction in forty-eight hours. Contact testing of the buccal mucous membrane with 200 U. crystalline penicillin G showed a moderate positive reaction after one hour of contact, persisting for twenty-four hours. The control contact tests were, all of them, negative.

The severity of such reactions is seen from the report of Morris and Downing[90] whose patient received 1,000,000 U. of penicillin for a postoperative infection. Itching of the left arm and hand was noted four days after the last injection, with an erythema and edema appearing twenty-four hours later; the edema being intense and progressing to the sixth injection day, at which time there were multiple ruptured and unruptured bullae, with multiple wheals affecting the left side of the face and the trunk. The bullous dermatitis disappeared in four to five days following bland therapy.

Since penicillin is derived from the mould Penicillium, it is not strange that relations to fungus infection should have been thought of early in the history of its use.

Lamb[71] treated a case of actinomycosis, which responded with a severe eruption and itching. Liberation of the toxins from the actinomycotic lesions may have caused the eruption. The patient gave positive reactions to intradermal tests with trychophytin and odiomycin, but not to penicillin. A second patient reacted positively to the intradermal test with penicillin but not to either trychophytin or odiomycin. Ten other control patients did not react to the intradermal tests with penicillin and the author suggests that all patients to be treated with penicillin should be questioned about the history of reactions to fungi. Those susceptible to the fungi should be tested intradermally with penicillin.

That some of the reactions may not be due to latent or associate trychophyton infections is suggested by Cormia[21] who elicited reactions in 2,000 soldiers as occurring in 0.5 per cent, one of the types of reactions being a simulating dermatophytosis. Of seventeen patients with fungus infections, who had never received penicillin therapy, fifteen gave immediate positive reactions to penicillin; none showed a delayed reaction; eight showed immediate and delayed reactions to trychophytin; and five only delayed to trychophytin. The patients who reacted to the intradermal tests with three brands of the commercial penicillin sodium showed immediate positive reactions in an average of 57 per cent. In this group, patients previously treated with penicillin by intramuscular or unguent use showed no greater tendency to positive reactions than did others. The reactions were considered to be non-specific and due to impurities, although crystalline penicillin also gave positive skin tests.

On the other hand, Schnurman[106] described five cases of latent trychophyton activated by the use of penicillin. All of the patients had previously been treated for a trychophyton infection and then for a secondary condition requiring intramuscular treatment with penicillin. For a period varying from three to thirty-six months following the penicillin injections, there was a recurrence of the trychophytin infection (which had apparently been cured).

Kolodny and Denhoff[69] studied twenty-one immediate and 11 delayed reactions among 124 patients treated with sodium penicillin. The immediate reactions were seen in twenty-five per cent of the dermatological patients as compared with 6 per cent of the general medial or neurosyphilitic patients. Of the eighteen dermatological patients, seventeen had exacerbations of the pre-existent skin conditions with pruritus, hyperemia and serum exudation. In four, a vesicular, pruritic "id" eruption appeared on the hands and feet. The incidence of reactions was highest in those with an eczematoid dermatitis. The delayed reaction was the same in both groups of patients and was typical in that it included urticaria, giant swelling, facial edema, lymphadenopathy, arthralgia, myalgia and malaise. In these patients there was no apparent relation to previous penicillin therapy, although in four cases contact dermatitis followed the local application of penicillin to previously treated skin areas. Of the fifteen patients who reacted to intradermal penicillin, 11 showed immediate positive tests to 1,000-2,000 U/0.1 c.c. solution. Nine subjects reacted to tyrothricin and eight of these to penicillin. Of the fourteen non-reactors, only two were sensitive by skin test. The tyrothricin skin test was positive in a high proportion of the penicillin-sensitive individuals and the severest reactions are said to have occurred in patients with fungus infections. The authors classify the immediate reactions as a dermatitis medicamentosa and the delayed reactions as typically allergic in nature, with the active principle of penicillin as the incriminating agent.

The most careful studies done by Cormia and Lewis[22] elicited the relationships between senstization to penicillin and pre-existing fungus disease. Following a series of eight experiments, the authors concluded that many of the local and systemic reactions occurring during or after penicillin therapy were the result of a previous sensitization by a dermatophyte. In forty-five children, aged two months to six years, who had never previously demonstrated fungus disease or received penicillin therapy, there was a non-specific immediate reaction after intradermal tests with 1,000 U. of penicillin, with no delayed forty-eight hour reactions. In seventeen patients, however, who presented active fungus disease, but had received no penicillin, immediate reactions occurred following intradermal tests with 41 per cent of the subjects, developing the forty-eight-hour tuberculin type of reaction. Of eight guinea pigs, five developed papular lesions following the second intradermal injection of penicillin given 28 days following the initial injection. In these five animals, the injection sites of the positive reactions were not flared up by intravenous injection of penicillin. There was no anaphylactic shock. Four of the five animals gave positive reactions to intradermal trychophytin injections. Five guinea pigs given weekly intradermal injections of trychophytin for four injections, followed a week later by intradermal injections of penicillin, did not develop sensitivities to either trychophytin or penicillin. A trychophyton gypseum infection induced in six guinea pigs resulted

in positive intradermal reactions to penicillin in three. In seven rabbits with trychophyton purpureum infection of the skin, five developed positive reactions to penicillin.

In a later paper, Cormia, Lewis and Hopper[23] evaluated the relationship between sensitization to penicillin and sensitization induced by superficial fungous disease by the Schultz-Dale test, using guinea pigs infected with T. gypseum or sensitized to penicillin. They demonstrated that in guinea pigs, anaphylactic sensitization to commercial sodium penicillin might be induced by a single injection given intradermally, or to crystalline penicillin sodium by a single intradermal, or four daily, intraperitoneal, injections. The guinea pigs could be sensitized anaphylactically to crystalline sodium penicillin G by infection of the skin with T. gypseum. These Schultz-Dale tests proved the presence of anaphylactic activity to commercial or crystalline sodium penicillin, in guinea pigs infected with T. gypseum. The authors feel that this positive reaction confirms the supposition that there is a common antigen in penicillin and the pathogenic fungi, which causes superficial fungous disease and that shock-like reactions in man are due to pre-exiting sensitization by such pathogenic fungi.

The case of a very serious allergic reaction from penicillin is described by Gelfand,[45] whose patient, a twenty-eight-year-old woman, received penicillin for the treatment of a postpartum infection, the dose being 300,000 U. beeswax-oil, followed twenty-four hours later by 50,000 U. in saline, both given intramuscularly. Twenty-four hours after the first injection, the patient responded with fever, headache, listlessness, myalgia, arthralgia, skin rash, edema, bronchial asthma and subconjunctival hemorrhages. The administration of penicillin was halted and PBZ in doses of 50 mg. was given thrice daily. The patient was improved within twenty-four hours, being discharged six days after the use of the drug had ceased. There was no history of previous allergy or drug reaction, excepting for an epidermophytosis of the toes. In this patient, intradermal and passive transfer tests with penicillin were negative.

There are a number of references to the aggravation of bacterids by penicillin. Heinlein *et al*[54] observed hypersensitivity reactions to penicillin in three patients with infectious eczematoid dermatitis, in three with eczema and in five with vesicular eruptions of the hands and feet, each with a history of symptoms of an underlying bacterial allergy, the symptoms being attributed to the rapid liberation of toxins from the focus of infection following vigorous penicillin therapy. In each case, the administration of standard doses of penicillin precipitated a hypersensitive reaction, aggravated the existing lesions and produced new eruptions. Although none of the patients in this series had received penicillin previously and all had proven negative skin tests for the antibiotics, in each the hypersensitive reaction occurred within a few hours or a few days after the initial dose. In one case there were positive skin tests to staphylococcus vaccine and to fungus extracts, but negative tests for penicillin. In a second there were positive tests with catarrhal and staphylococcus vaccines with a negative test to penicillin; the third, like the first, gave positive tests to the fungus extracts and the staphylococcus vaccine, but did not react to penicillin. The symptoms did not appear until the sixth day and included a leucopenia with a lymphocytosis instead of leucocytosis with a neutropania.

Typical specific effects on bacterial responses are, of course, seen in Herxheimer reactions. Moore *et al*[87] listed such reactions as occurring in 50 per cent of 418 cases of early syphilis. In Leifer's series[73], the total was 87 per cent. In late syphilis, Stokes[118] reported forty-three (24 per cent) of 182 cases. In twenty-three of these, fever was the only reaction, but in several, transverse myelitis, Jacksonian convulsions, exacerbation of pain in tabes dorsalis, mania and hallucinations were seen. It is of interest that Herxheimer reactions have served to delineate the protean nature of lues, as seen by the case described by Scot and Clark[108] which demonstrates that "some clinical involvement of the kidney exists in early syphilis and that a focal Herxheimer reaction, affecting a subclinically involved renal parenchyma, may produce a nephrotic syndrome (syphilitic nephrosis)." The patient who had suffered a penile lesion on July 15 was admitted for antiluetic treatment on September the first, at which time he presented a generalized papular rash, the lesion being positive for T. pallidum. The physical examination was otherwise negative, there being no urinary abnormalities. The Kahn blood titer was 200 units and the cerebral spinal fluid negative. Treatment with penicillin was initiated, with 50,000 U. being given intramuscularly at two-hour intervals. Six hours after beginning treatment there was a temperature elevation; and again on the third day of therapy with nocturia on the second treatment day. The patient was given 4,800,000 U. of penicillin in eight days and five days after his discharge, demonstrated swelling of the legs and genitalia, at which time examination revealed a marked proteinuria, cylinduria, a low plasma albumin with inversion of the albumin-globulin ratio, massive edema, elevated blood cholesterol, subnormal basal metabolic rate and normal renal function tests, with no

hypertension, retinitis or hematuria. Following the use of a salt-free diet, the patient lost 30 pounds in five days with the disappearance of the edema, the urine becoming protein-free. It took about three months for the urine and blood chemistry to become normal, with the Kahn titer gradually declining to four units 130 days after hospitalization.

The case described by Cole *et al*[19] is interesting in that a Herxheimer reaction followed the first injection of penicillin and the authors not only describe local pain at the injection site, with urticaria, erythema multiforme-like eruptions on the extremities, but also an erythema nodosum-like eruption of the shins. Olansky[95] describes a severe febrile Herxheimer reaction in six patients following a single dose of 1,000 U. of penicillin. In three there was a diagnosis of secondary syphilis; in one congenital paresis, in one a gumma of the testicle, and in one later hypertrophic syphilides of the vulva.

Crawford[24] suggests that this reaction can be avoided by the administration of one-fourth or one-half the usual dose and by giving patients with late or complicated lues a course of bismuth prior to the penicillin therapy.

Penicillin can, of course, cause central nervous system effects. Early in 1945, Walker and Johnson[134] described convulsive effects following intraventricular injection in the treatment of meningitis. Preliminary studies show that penicillin, administered intracisternally, intraventricularly, and locally to the cerebral cortex in certain doses produces convulsive manifestations in mice, cats, dogs and monkeys. Penicillin from seven manufacturers was used with similar results, the intracortical injection of penicillin producing convulsive seizures in cats, monkeys and humans. Control injections with isotonic sodium chloride or 95 per cent alcohol caused no deleterious effects. The pH of the solution was not responsible and the convulsive seizures were apparently related to the high dosage. The convulsive factor was affected by aging, boiling, and the level of dosage in man was about 20,000 U., which produced electroencephalographic changes but no clinical symptoms. Ten thousand units injected near the motor area produced twitching of the face and hands for three hours. The authors feel that injections of penicillin into wounds or abscesses may, however, prevent the diffusion of the drug to the adjoining nerve tissue. The convulsive factor may, on the other hand, limit the amount of penicillin injected into the cisterna magna and the cerebral ventricles.

The problem is reviewed by Walker, Johnson and Kollnos,[135] who describe penicillin given intrathecally in high concentration as causing multiple hemorrhages, severe inflammatory reactions and transverse myelitis. They review other effects such as peripheral neuritis and convulsions as observed in a patient with a latent epilepsy, who had specific electroencephalographic changes. This subject was given penicillin intramuscularly for an incidental condition. The authors state that toxicity is manifested by an acute necrosis involving the adrenal glands, particularly the cortex and suggest that some of the unexplained deaths in human beings occurring during the administration of penicillin may be of this type since the autopsy findings, in a few instances, do not mention adrenal damage. They quote Furth as suggesting that functional impairment of the adrenals may precede objective evidence of damage and may cause death without the confirmation of definitive pathological findings. According to Sweet *et al*[123], mild and severe radiculitis may follow intrathecal injections of penicillin, with all of the patients making a full recovery.

In Simon's case[116] the patient, a five-day-old infant, was prepared for the removal of an meningomyelocele with 100,000 U/20 c.c. saline being placed in the subarachnoid space. A second injection of 100,000 U. twenty minutes later into the lumbar muscle was followed by convulsions, cyanosis, and apnea. The symptoms were controlled by the administration of oxygen, which was given for three hours. Consciousness was restored at this time and attributable by the author to the depletion of the penicillin in the blood. Neymann (in a discussion of a paper by Johnson *et al*[60]) states that intraventricular and intracisternal injection of penicillin in man may induce a status epilepticus with a fatal outcome. In a later paper, Walker and his co-authors[133] call attention to the toxic effects of penicillin on the nervous system, showing that although electroencephalographic findings were normal in 40 per cent of fifty-one cases receiving systemic penicillin for conditions other than those primary to the central nervous system and although there appears to be a relatively wide margin of safety between the antibiotic concentration and the convulsive threshhold of penicillin and also streptomycin, the toxic effects of penicillin and of other antibiotics on the nervous system must be taken into consideration. Tests with actinomycin and clavacin, as well as with streptomycin and streptothrycin all produced convulsive manifestations when injected into the cerebral cortex of cats or monkeys. Epileptic attacks have been produced in monkeys by application of 250 units to the cerebral cortex.

According to Kolb and Gray[68] intramuscular administration of penicillin may cause localized peripheral neuritis as seen in seven cases. The neuritis occurred from ten to twenty-one days after the initial injection and after ten to seventy-two injections representing a dose of 200,000-2,000,000 units. Both sensory and motor disabilities were observed in three cases affecting the peroneal nerve, in one the sciatic nerve and in two the nerves of the brachial plexus. All injections were given in the gluteal and thigh regions. In only one instance could the neuritis have resulted from the direct infiltration of penicillin into the nerve itself. Sensory function was recovered in eight weeks; motor function in four months, although motor weakness persisted for seven months in the patients with brachial palsy. No evidence was observed that the neuritis was related to the brand of penicillin used, to compression or to allergy to penicillin.

Erickson, Masten and Suckle[36] described the complications of intrathecal use of penicillin and added their four cases of serious reactions to those in the literature, suggesting that such complications may be avoided by using dilute solutions, with the number of intraspinal injections being kept at a minimum, with greater reliance being placed on early treatment with maximum doses of penicillin given parenterally. Morginson[89] lists the intrathecal reactions as including headache, vomiting, vascular collapse, cyanosis, convulsions, unconsciousness, flaccid paralysis of the extremities, with increased spinal fluid cell count and protein values.

That toxic psychoses may result from penicillin therapy is demonstrated by the report of Kline and Highsmith[67], whose patient, an eighteen-year-old girl, received penicillin for the treatment of an upper respiratory illness, 48,000 U. being given intramuscularly in thirty-six hours. One year later, for the treatment of an otitis media, she received 420,000 U. intramuscularly and 3,800,000 U. orally in ten days. Two days after conclusion of the second course of treatment she was re-admitted to the hospital with a temperature of 101°F, generalized urticaria and an arthralgia of the fingers, knees and ankles. The neurological examination was negative. The urticaria responded to the administration of PBZ every four hours, the arthralgia subsiding after novocaine injections. On the fourth hospital day, the patient became restless, suspicious, and complained of hearing voices. Although the PBZ was discontinued with an exacerbation of the urticaria the mental symptoms became more pronounced. With the re-institution of antihistaminic treatment, the hives subsided and within two days the mental symptoms disappeared. The authors feel that the mental symptoms were due to edematous lesions of the brain resulting from a localized penicillin sensitivity.

It is essential to realize that secondary reactions affecting the blood and urine may confuse the laboratory studies in patients receiving incidental antibiotic treatment. Macht[77] has demonstrated that streptomycin and all brands of amorphous penicillin produce a marked acceleration in the clotting time of the blood in rabbits and cats, irrespective of the means of injection, with penicillin G having only a slight thromboplastic effect, K a still greater and penicillin X the greatest effect. A small amount of penicillin X has a synergistic effect when injected in a mixture with penicillin G. The effect is usually seen fifteen to twenty minutes after injection, but may be delayed one hour. In rabbits, the clotting time is shortened for long periods, but usually approximately one hour. This thromboplastic action may be neutralized by Dicoumarol administration orally. Fleming and Fish[39] have shown the coagulation time of human blood *in vitro* is increased and contraction of the clot retarded by both crystalline and impure penicillin. The greater the concentration in the blood the longer the coagulation time. The results, however, do not pertain to systemic administration of penicillin because with such therapy the concentration of the drug is very low. The local administration of penicillin in concentrations exceeding 100 U/ml might interfere with coagulation and clot contraction.

Although not completely conclusive a paper by Spain and Clark[117] demonstrates the possibility of agranulocytosis occurring during a course of therapy in a patient in whom penicillin was given preoperatively and postoperatively for a cecostomy. The third day postoperatively the patient demonstrated a generalized erythematous macular rash, with a temperature rise to 104°F, with a white cell count which dropped from an initial 13,150 to 2,800 and then to 100 by the fourth day. Penicillin was discontinued, a blood transfusion given and sulfadiazine substituted for the antibiotic agent with a rise in white cell count to 6,000 and a temperature drop to 101°F within sixteen hours. The patient died on the third day. The autopsy revealed no abnormalities of the bone marrow. The authors feel that although the relationship is inconclusive, the signs point to penicillin as being the causative agent.

Although reactions in large variety have followed penicillin therapy, some may, of course, not be due to penicillin. In a few instances, the relationship to other causes

was known or could be surmised. Of the number of such, the following miscellaneous additions have been chosen.

In 1946, hepatitis was described as being a sequel to penicillin injections. As described by Howells and Kerr[58] the period between injections and the onset of icterus ranged from sixty-two to 157 days, with an average of ninety-seven days. The jaundice lasted from ten to forty-four days with an average of twenty-one days, and the period of hospitalization was fifteen to forty-nine days, with an average of thirty days. Hughes[59] described the development of infectious hepatitis in twenty-three of 144 patients and in ten of sixty-six patients being treated with penicillin injections for bone infections. The syringe was found contaminated with red blood cells, due either to back pressure from the contracted muscle, spread of blood from the needle to the syringe or suction when removing the needle from the syringe. Since injections had been given to several patients with the same syringe, with only a change of needle, it is possible that one patient could be infected with hepatitis from another. Of the 124 cases of hepatitis admitted, thirty-six had received penicillin injections within the preceding seven months. In ten cases, it was possible that the jaundice was post arsphenamine or hemologic serum jaundice, but in 21 per cent of twenty-six cases, the jaundice was considered as subsequent to the penicillin treatment.

Other types of secondary reactions may follow penicillin injections as seen in the report of Ebrill and Blek[33], whose patient, an eleven-year-old boy, receiving penicillin by continuous intramuscular administration for the treatment of a large, painful abscess of the right axilla developed a tuberculous abscess at the point of the injection. There was no possible source of tuberculous infection in the patient and it was concluded that the tubercle bacilli had gained access to either the penicillin powder, the solution or the injection apparatus through the faulty technique of the individuals preparing them.

The cases reported by Harris *et al*[52] describe a bacillus pyocyaneous infection occurring in four patients, who received penicillin treatment. The first, a patient with pneumococcus (Type 18) meningitis received penicillin intramuscularly and intrathecally with a return of temperature to normal and with a subsequent elevation. The postmortem examination showed the spinal fluid culture to contain B. pyocyaneous. The second patient presented a similar clinical course, as did the third and fourth, who, however, survived. It is discovered that a closed jar used to store sterilized syringes used for the intramuscular injections of penicillin harbored B. pyocyaneus. The syringes became contaminated and therefore contaminated the stock penicillin used. No abscesses, however, occurred at the site of intramuscular injection in any of the cases. The authors suggest that syringes be kept separate and autoclaved, that individual vials of penicillin and of saline be used for each patient, and that the caps of the vials be washed with individual iodine and alcohol swabs before being punctured.

The case described by Mitchell, Pordy and Wallach[55] concerns the occurrence of a bacillus welchii, gas gangrene at the site of penicillin intramuscular clysis in a fifty-one-year-old woman who was found to possess a positive blood culture of Staphylococcus aureus. Eighteen days after initiation of treatment the site of penicillin infusion showed tender, swollen, hard, crepitant fluculant masses, the culture from which yielded B. welchii. The patient was given gas gangrene antitoxin and the area widened and treated locally with hydrogen peroxide, penicillin instillations and packs, responding to treatment.

Since penicillin in oil or beeswax is being used in decreasing amounts, the reactions due to the composition and method of administration can well be omitted at this time, excepting to remind ourselves that pulmonary embolism may follow such treatment. The patient described by Bondy *et al*[11] was an eighteen-year-old negress suffering acute pulmonary distress evidently owing to an obstruction to the flow of blood through the pulmonary vascular bed within twenty-four hours after an accidental intravenous injection of 2 c.c. of a mixture containing 600,000 of penicillin calcium suspended in peanut oil containing 4.8 per cent white wax. This led to animal studies which indicated that peanut oil and peanut oil-miner oil could be demonstrated in the capillaries of the lung while the beeswax mixture was trapped in the larger branches and pulmonary arteries. The animals were sacrificed at intervals of five minutes and twenty-four, forty-eight and seventy-two hours after the intravenous injection of the various mixtures and it was shown that the most severe emboli were produced by the beeswax mixture. The granuloma produced by the beeswax-peanut oil mixture resembled that produced by lipoid pneumonia. The animals given fatal doses of peanut oil exhibited cerebral involvement, while lethal doses of peanut oil-beeswax produced pulmonary edema without evidence of peripheral emboli.

It was known in 1945 that massive doses of penicillin caused highly positive quali-

tative albumin reaction in rabbits, who received massive doses of penicillin, although they had previously demonstrated negative albumin urinalysis. Perlstein *et al*[97] state that the addition of 25 per cent, by volume, of acetone or ethyl alcohol to 5 c.c. of urine will prevent these pseudo-albumin reactions, providing that less than 10 to 13 mg. of penicillin is present in the urine. Pseudo-glycosuria has also been described as sequential to penicillin therapy by Boldref[10] who describes two patients, both of whom gave positive urine sugar reactions. The author demonstrated that a penicillin solution, 100 U/c.c. reduced the copper sulfate of Benedict's solution *in vitro*. Nylen[92] warns that impairment of renal function should be watched for in the course of penicillin therapy on the basis of a patient whose partial anuria following sulfathiazole treatment progressed to complete anuria with penicillin therapy. Such reactions, if true, must indeed be rare.

For a physician confronted with a case of penicillin sensitivity the paramount problem is one of treatment. He is faced with two problems, the patient's original illness which requires penicillin therapy and the reaction to penicillin which needs treatment in its own right. Unfortunately, the reactions of penicillin are so protean in their nature, the types of penicillin so many and the variation from lot to lot and from manufacturer to manufacturer so different that no clear-cut definite method of treatment, applicable to all patients and all types of reactions, exists. The problem is especially complex because new types of penicillin and new methods of administration appear with bewildering succession, each claiming to be more free of reactions than its predecessors.

In five patients studied by Callaway and Barefoot[15] search was done for evidence of the presence of penicillin antibodies in cases of urticaria. All intracutaneous and passive transfer tests were negative, although in the precipitin tests in all instances, including the control tests, a fine precipitate was noted at the junction of the serum and penicillin solutions. The authors state that the results were inconclusive and also, since in all instances the urticaria was controlled by Benadryl, the hives may be explainable as due to the presence of an excessive amount of histamine, but from the studies reported, not present as an antigen-antibody reaction.

Farrington and Tamura[38], however, describe immediate urticarial reactions to intradermal tests with crystalline penicillin G and K. The reaction appeared two to five minutes after injection and consisted of an accentuation of the original injection wheal, manifested by a slight central edema and a spreading erythema usually receding in an hour. The authors state that they have encountered no associated generalized urticaria or constitutional symptoms with the method, the immediate reaction of this type proving helpful in about 24 per cent of the cases. The authors stress the point that correlation of cutaneous testing, penicillin therapy and reactions depend upon many factors, including the site, the rate and the number of antibodies formed and suggest that testing be done with diluted solutions, the degree of sensitivity being ascertained by quantitative tests using 2.5-2,000 U/0.1 c.c. normal saline. They believe that a significant degree of sensitivity is indicated by a reaction with a diameter over 1.5 cm. with 2.5 U of crystalline penicillin. The truly positive immediate reaction is almost invariably followed by hypersensitivity reactions to penicillin in therapeutic doses. Simultaneous testing with various penicillin products indicate the one most likely to be tolerated.

Although the penicillin-oil-beeswax type of treatment is no longer in general use, the question of sensitivity to the medium is worthy of brief mention. According to Gay[44] the beeswax is not antigenic. On the other hand, Watson[137] has shown that a bee keeper who was given six injections of 250,000 U. penicillin-oil-wax for the treatment of a carbuncle, responded on the eighth day after the first injection with reactions of the sites of the old bee stings, although she had not reacted to an aqueous solution previously given her.

That sensitivity may be associated with different lots of the drug is illustrated by the report of Barefoot and Orlansky[3], whose patient responded with urticaria to non-crystalline penicillin therapy responding six hours following the first injection with an urticaria followed in twenty-four hours by generalized erythema lasting twenty-four hours more. Ten days later the patient developed a generalized furunculosis and non-crystalline sodium penicillin treatment was resumed with 20,000 U. every three hours, the patient responding after five doses with generalized erythema and edema of the skin and an exacerbation of a chronic tinea cruris and a chronic dermatophytosis. Skin tests with crystalline and non-crystalline penicillin in 1,000 U/c.c. in saline showed a 2 cm. area of erythema with induration to the first, with none to the second. The patient was given crystalline penicillin every three hours with no untoward effects. The authors report three other patients who could not tolerate non-crystalline penicillin but could take crystalline penicillin G.

Peck and his associates[96] described an apparent successful desensitization to penicillin in a sixty-three-year-old male who responded to intramuscular penicillin by an erythematovesicular eruption appearing on the hands, feet and groin, rapidly becoming generalized. In this case, intradermal tests with crystalline penicillin were positive. The patient was given subcutaneous injections of penicillin three times weekly, beginning with a dose of 400 units and doubling each dose until 12,000 U. was being injected by the end of the second week, the dose gradually being increased to 20,000 U. After provocative intramuscular injections of 5,000; 10,000; and 30,000 U. were given without untoward effects, a treatment regimen of 30,000 U, three hourly, was begun. A cutaneous reaction appeared after the fourth injection. The penicillin was discontinued for forty-eight hours and then resumed in smaller doses of 10,000 U/3 hourly, the dose being taken by the fourth day to 30,000 U, which was continued at this level at three-hourly intervals for seventeen days without reaction. Skin tests at that time to both crystalline and commercial penicillin were negative.

Desensitization has also been used for contact dermatitis[103] injections of 0.05 c.c. of a solution containing 10 U. c.c. being given thrice weekly, increasing the dosage gradually as in pollen desensitization. After a dose of 1 c.c. is reached with the 100-unit/c.c. solution, increasing concentrations of 1,000; 10,000; and 100,000 U/c.c. should be used. If a dermatitis develops during treatment, the dose should be reduced. The application of a PBZ-containing ointment before having penicillin may prevent the development of the dermatitis.

Intravenous nicotinic acid in doses of 35 mg. in 10 c.c. of distilled water has been reported by Service[112] as controlling urticaria in forty-one cases of penicillin sensitivity. The antihistaminic drugs have all been used with varying success. Wilcox[140] treated six cases of urticaria with Benadryl in doses of 50 mg. t.i.d. In four cases the urticaria cleared in one to three days, although the usual severe reaction lasted four or more days. One patient was treated successfully with ephedrine. In one case, however, the concomitant use of Benadryl and epinephrine caused collapse and both drugs had to be discontinued. Dean's patient[28], who had responded with urticaria, pruritus, dyspnea, enlargement of axillary and inguinal glands and an expiratory wheeze, was rapidly relieved by the oral administration of 100 mg. of Benadryl, as an initial dose, followed by 50 mg, six hourly.

A patient described by Kampmeier[61] had reacted to a third course of penicillin therapy with pruritus, urticaria and edema of the hands, an intradermal test to the penicillin used being positive. PBZ in the 40 mg. dose two hourly, given orally, controlled the edema in four hours, making the patient asymptomatic in twelve hours.

Gelfand[45] also used PBZ in 50 mg. doses after an initial 150 mg. with improvement noted in forty-eight hours.

In Barach's[2] series of 51 patients treated for pulmonary conditions with the aerosol type of therapy, treatment for unfavorable reactions is noted as being controlled by PBZ, Benadryl or Vitamin K. An increase in dyspnea as a reaction to the aerosol penicillin was treated by substitution with systemic injection therapy. Lubowe[74] treated a severe diffuse erythematous maculopapular eruption, involving the face, chest, back and extremities and associated with a marked area of induration and swelling at the site of injection in a patient given 300,000 U/crystalline penicillin G in beeswax-peanut oil with Thephorin in doses of 200 mg. daily with complete disappearance of the symptoms after five days.

The number of cases in which the antihistaminic agents do not have any effect are rarely reported. In the author's own personal experience with urticaria and aggioneurotic edema following procaine penicillin G suspended in peanut oil containing 2 per cent of aluminum monostearate no alleviation of symptoms occurred following the ingestion of 500 and 100 mg. doses of PBZ, Thephorin, thenylene, Neohetramine, Decapryn, with mild alleviation following ingestion of Trimeton. Demerol in 50 mg. and 100 mg. doses given subcutaneously was the drug which controlled the associated pruritus, having no effect upon the urticaria or angioneurotic edema, which lasted five days.

The two cases described by Davis[27] also failed to respond to anti-urticarial drugs of either the antihistaminic or sympathomimetic type.

Rossellini and Van Rooy[104] reported a delayed reaction to penicillin in oil and wax as treated with procaine intravenously, 1 gm. in 500 c.c. of isotonic saline being given in two hours. After the second infusion, the following day the patient was symptom-free. The symptoms had lasted for three days before treatment had started and since the average case of urticaria lasts approximately five days, all reports of successful treatment must take this into consideration. In the patient described by Dressler and Dwork[31] the patient reacted with urticaria and fever to a second course of penicillin, the symptoms not responding to 250 mg. of Benadryl given in divided doses.

The symptoms included a rash, generalized pruritus, sore throat, arthralgia, and a high leukocyte count. Calcium gluconate and epinephrine had no effect, but 1 gm. procaine and hydrochloride in 500 c.c of isotonic saline by intravenous drip resulted in the disappearance of all the hypersensitivity symptoms in twenty-four hours. Cutaneous tests to penicillin sensitivity given nine days later were negative.

Cohen and Kaufman[17] also used the State and Wagensteen Method of treating penicillin sensitivity with procaine hydrochloride, two of their four cases not responding. One patient, who developed angioneurotic edema, urticaria, myalgia, arthralgia and fever ten days after having taken penicillin did not respond to Benadryl, PBZ, intravenous calcium thiosulfate, Vitamin B, Vitamin K, Demerol, phenobarbital, atropine, codeine, aspirin, intravenous nicotinic acid, intravenous glucose, autohemotherapy, or procaine hydrochloride. Repeated injections of epinephrine alone gave temporary relief. In the second patient, intravenous calcium gluconate relieved the itching, although Benadryl and intravenous procaine were of no benefit.

Waldbott[132] warns that a possible fatal reaction may follow the use of procaine in sensitive subjects. One patient was given 0.5 Gm. of procaine hydrochloride in 250 c.c. of saline solution intravenously developed a severe allergic shock. Patients with chronic urticaria are most apt to be sensitive to the drug and the preliminary skin tests are unreliable when the skin is the site of urticarial lesions.

At the present time information concerning penicillin reactions may be summarized as follows: "The reactions occur most frequently in patients who have had several courses of penicillin. The continuation of penicillin treatment of a patient who has reacted with urticaria may or may not be tolerated. Skin tests are unreliable in predicting the occurrence of reactions and the antihistaminic drugs may or may not control the reactions and permit continuation of penicillin therapy." Pillsbury and his associates[99] state that the urticaria reactions may be persistent and severe and may be accompanied by asthma and may be followed by ecchymoses and uterine bleeding. It is their opinion that the incidence of urticarial reactions is increasing as suggested by the fact that 1.8 per cent of reactions occurred in the first 824 cases of syphilis treated at the University of Pennsylvania, whereas twelve cases have occurred in the last 200 patients treated between October, 1945 and May, 1946. Of twenty-three cases of urticaria treated with antihistaminic drugs, sixteen with Benadryl were relieved in fourteen; with no relief in two and seven treated with PBZ showed relief in two and none in five. In their opinion, penicillin must be halted as soon as a reaction occurs, unless there is immediate critical need of the drug. Antihistaminic agents should be given by mouth three times daily or slow intravenous injection in isotonic saline is advised if the reaction is severe. After subsidence of the urticaria or the accompanying symptoms, a test dose of another brand of penicillin (1,000 U.) may be given, while the antihistaminic drug is continued by mouth. If there is no reaction in six hours, a second dose of 10,000-20,000 U. can be used followed by the full therapeutic dose if there is no reaction within four hours. The antihistaminic drugs should be continued and gradually reduced over a period of two to three days. No compounds prolonging the serum level of penicillin should be used during the period of trial administration. If re-administration is impossible and therapy is desirable, cautious administration should be resumed after an interval of four or more weeks.

It is, of course, too soon to judge the new types of penicillin, although preliminary reports for penicillin O indicate that it is probably less sensitizing than the other types now generally available. It is hoped that future studies and reports will be made by physicians trained in the field of allergy and immunology and familiar with the technique for testing sensitivity, defining it if such sensitivity occurs. A number of the earlier papers are confused and unreliable because they were made by the physicians using penicillin for the treatment of infectious conditions. These workers were only secondarily expert in recognizing and testing for sensitivity. It is hoped that future studies will be done by experts in the field of allergy. Had this course been followed, a great deal of time would have been saved and a great many patients spared reactions.

BIBLIOGRAPHY

1. Anderson, A. B.: Anaphylactic purpura following intramuscular penicillin therapy. M. J. Australia, 34:305-306, (March 8) 1947.
2. Barach, A. L., Garthwaite, B., Levenson, E. and Rader, D.: Physiologic and antibiotic (penicillin) therapy in chronic hypertrophic pulmonary emphysema. Dis. Chest, 13:91, (March-April) 1947.
3. Barefoot, Sherwood W. and Orlansky, Sidney: Report of a patient tolerating crystalline penicillin without reaction after repeated reactions to crude penicillin. North Carolina M. J., 8:82-83, 1947.
4. Barker, A. M.: Allergic reactions to penicillin. Lancet, 1:177, (Feb. 10) 1945.
5. Bedford, P. D.: Black tongue and oral penicillin. Brit. J. M., 2:63, (July) 1946.

6. Bedford, P. D.: A case of penicillin dermatitis. Brit. M. J., 1:51, (Jan. 12) 1946.
7. Benkwith, K. B.: Allergy to penicillin calcium topically in blepharoconjunctivitis. U. S. Naval M. Bull., 46:279, (Feb.) 1946.
8. Binkley, George W. and Brockmole, Arnold.: Dermatitis from penicillin. Arch. Dermat. & Syph., 50:326, (Nov.) 1944.
9. Blechmann, G., Courtois, J. and Auclair, J. M.: Local reactions due to slowly absorbed (oil-beeswax) penicillin in two infants. Societe Medico-Chirurgicale des Hopitaux Libres *through* Presse med., 56:31, (Jan. 10) 1948.
10. Boldyref, E. B.: Occurrence of pseudo-glycosuria in patients treated with penicillin. J.A.M.A., 133:715, (Mar. 8) 1947.
11. Bondy, Philip K.: Sheldon, Walter H. and Weens, H. Stephen.: Pulmonary embolism caused by penicillin-oil-beeswax. Am. J. Med., 3:34-43, (July) 1947.
12. Brown, R. L.: Glossodynia and exfoliation of papillae filaments after oral administration of penicillin. Arch. Otol., 45:355, (March) 1947.
13. Burt, C. E. and Caplan, S. M.: Unusual reaction to penicillin in oil and wax. New England J. M., 238:804, (June 3) 1948.
14. Call, R. A., and Gilbert, R. A.: Sensitivity to penicillin resulting in abscess formation. J.A.M.A., 134:1475, (Aug. 23) 1947.
15. Callaway, J. L. and Barefoot, S. W.: Immunological studies on patients developing urticaria association with penicillin therapy. J. Invest. Dermat., 7:285, (Dec.) 1946.
16. Canizares, O.: Is penicillin a photosensitizing agent? Arch. Dermat. & Syph., 52:17, (July) 1945.
17. Cohen, A. E. and Kaufman, J.: The use of procaine hydrochloride intravenously in the treatment of reactions to penicillin. J. Allergy, 19:68, (Jan.) 1948.
18. Cohen, T. M. and Pfaff, R. O.: Penicillin in dermatologic practice. Arch. Derm. & Syphil., 51; 172-177, (March) 1945.
19. Cole, H. N.; Ayres, S.; III, Barr, J. H.; Genatiod, T.; Held, B.; Murphy, W. W.; Printz, D. R.; and Strauch, J.: Use of penicillin in the treatment of syphilis in pregnancy. Arch. Dermat. & Syph., 54:255, (Sept.) 1946.
20. Cook, T. J.: Stomatitis following the use of penicillin troches. Oral Surg., Oral Med., & Oral Path., 1:265, (March) 1948.
21. Cormia, F. E.; Jacobsen, L. Y.; and Smith, E. L.: Reactions to penicillin. Bull. U. S. Army, 4:694, (Dec.) 1945.
22. Cormia, F. W., and Lewis, G. M.: Experimental aspects of penicillin sensitization with special reference to conjoint sensitization to superficial fungous disease. J. Invest. Dermat., 7:375, (Dec.) 1946.
23. Cormia, F. W., and Lewis, G. M., and Hopper, M. E.: Experimental aspects of penicillin sensitization: II With reference to the Schultz-Dale phenomenon. J. Invest. Dermat., 8:395, (June) 1947.
24. Crawford, M. G.: The treatment of syphilis. A review. New England J. M., 238:152-160, (Jan. 26) 1928.
25. Criep, Leo H.: Allergy to penicillin, J.A.M.A, 126:429-430. (Oct. 14) 1944.
26. Cuthbert, J. C.: Allergic reactions to penicillin. (Letter). Brit. M. J., 1:823, (June 7) 1947.
27. Davis, Ernest D.: Toxic reactions of penicillin. Cincinnati J. Med., 28:321, 1947.
28. Dean, Geoffrey, Benadryl treatment of penicillin allergy. (Letter). Brit. M. J., 1:823, (June 7) 1947.
29. Derzavis, J. L., and Beinstein, J.: Hemorrhagic gangrenous exfoliative dermatitis following penicillin in oil and beeswax; combined immediate and delayed reactions. Report of a case. M. Ann. District of Columbia., 17:32, (Jan.) 1948.
30. Dolan, R. A.: Severe delayed reaction to penicillin. Canad. M. A. J., 57:167, (Aug.) 1947.
31. Dressler, Sidney and Dwork, Ralph E.: Reactions to penicillin. J.A.M.A., 133:849, (Mar. 22) 1947.
32. Duemling, Werner W.: Clinical experiences with penicillin in the Navy. Ann. New York Acad. Sc., 48:201-218, (Sept. 27) 1946.
33. Ebrill, D., and Blek, S. D.: Tuberculous abscesses following intramuscular penicillin; report of a case. Lancet, 2:379, (Sept. 14) 1946.
34. Eisenstadt. W. S.: Hypersensitivity to penicillin simulating serum sickness. Minnesota Med., 29:689, (July) 1946.
35. Ellinger, P., and Shattock, F. M.: Black tongue and oral penicillin. (Correspondence). Brit. M. J., 2:208, (Aug. 10) 1946.
36. Erickson, T. C.: Matson, M. G.; and Suckle, H. M.: Complications of intrathecal use of penicillin. J.A.M.A., 132:561. (Nov. 9) 1946.
37. Farrington, M.D., Dickersman, F. A., and McGowan, W. L.: Observations on variations in reactivity in a case of allergy to penicillin. Ann. Allergy, 6:30-32. (Jan.-Feb.) 1948.
38. Farrington, J., and Tamura, J.: Cutaneous testing in a case of exfoliative dermatitis caused by penicillin. Arch. Dermat. & Syph., 56:807, (Dec.) 1947.
39. Fleming, Alexander and Fish, E. W.: Influence of penicillin on the coagulation of blood, with especial reference to certain dental operations. Brit. M. J., 2:242-243, (Aug.) 1947.
40. Flinn, Lewis B., McGee, Lemuel C., Featherston, William P., and Kern, Douglas O.: Skin lesions attending the use of penicillin. Delaware M. J., 17:133-135. (July) 1945.
41. Florey, M. E., and Florey, H. W.: General and local administration of penicillin. Lancet, 1:387-97, (March) 1943.
42. Freyhan, Fritz A.: Pruritus—A side-effect of penicillin therapy. Delaware M. J., 16:177-179, (Nov.) 1944.
43. Friedlaender. S., Watrous, R. M., and Feinberg, S. M.: Contact dermatitis from penicillin; the source of the antigen. Arch. Dermat. & Syph., 54:517, (Nov.) 1946.
44. Gay, L. N.: Non-antigenic Property of Beeswax. J. Allergy, 16:192, 1945.
45. Gelfand, Maxwell L.: Allergic reaction to penicillin. New York State J. Med., 47:2707-2708, (Dec. 15) 1947.
46. Gent, J. C., Mackinnon, Kenneth: Severe reactions to penicillin. Brit. M. J., 1:665, (Apr. 3) 1948.
47. Goldman, Leon: Cheilitis from local use of penicillin solutions in the mouth. Arch. Dermat. & Syph., 53:133-134, (Feb.) 1946.
48. Goldman, L.; Friend, F., and Mason, L. M.: Dermatitis from penicillin. J.A.M.A., 131: 833, (July 13), 1946.
49. Gordon, E. J.: Delayed serum sickness reaction to penicillin. J.A.M.A., 131:727, (June 29) 1946.
50. Gottlieb, I., and Frankland, A. W.: Urticarial reactions to penicillin. Lancet, 253:36, (July 5) 1947.

51. Grolnick, Max and Loewe, Leo.: Immunologic studies in patients with subacute bacterial endocarditis treated by combined penicillin heparin method. J. Allergy, 18:277-282, (July) 1947.
52. Harris, R. D.; Buxbaum, L.; and Applebaum, E.: Secondary bacillus pyocyaneus infection in meningitis following intrathecal penicillin therapy. J. Lab. & Clin. Med., 31:1113, (Oct.) 1946.
53. Haswell, R. E., and Wilkinson, J. F.: Allergic reaction to parenteral penicillin. Lancet, 1:308, (March 2) 1946.
54. Heinlein, J. A., Carpenter, C. C., and Duffy, B. J., Jr.: Aggravation of bacterids by penicillin. U. S. Nav. M. Bull., 46:471, (April) 1946.
55. Hinman, A. T., Warner, C. F., and Li, J. G.: Delayed reactions following penicillin therapy. California Med., 65:112, (Sept.) 1946.
56. Holden, Eugene M.: Allergic reaction to penicillin. New England J. Med., 236:796-798, (May 22) 1947.
57. Hopkins, J. Gardner and Lawrence, Herbert: Sensitization to penicillin. J. Allergy, 18: 251-262, (July) 1947.
58. Howells, L., and Kerr, J. D. O.: Hepatitis after penicillin injections. Lancet, 1:51, (Jan. 12) 1946.
59. Hughes, R. R.: Post-penicillin jaundice. Brit. M. J., 2:685, (Nov. 9) 1946.
60. Johnson, H. C., Walker, A. E., and Case, T. J.: The effects of penicillin on the central nervous system. Arch Neurol. & Psychiat., 54:160, (Aug.) 1945.
61. Kampmeier, R. H.: The use of Pyribenzamine hydrochloride in controlling urticaria due to penicillin. Am. J. Syph., Gonor. & Ven. Dis., 31:57, (Jan.) 1947.
62. Keefer, C. S., Blake, F. G., Marshall, E. K., Jr., Lockwood, J. S., and Wood, W. B., Jr.: Penicillin in the treatment of infection (500 cases). J.A.M.A., 122:1217-24, (Aug.) 1943.
63. Kendig, Edwin L., and Toone, Elam C., Jr.: Delayed serum type of reaction to penicillin. South. M. J., 40:607, 1947.
64. Kerfoot, T. H.: Use of penicillin pastilles. Brit. M. J., 1:197, (Feb. 1) 1947.
65. Kern, E. C.: Local reaction to penicillin given by mouth. J. M. S., New Jersey, 42:326, (Oct.) 1945.
66. Kleinfeld, L.: Sequelae following oral and topical use of penicillin. New York State J. Med., 46:915, (Apr. 15) 1946.
67. Kline, C. L., and Highsmith, La R. S.: Toxic psychosis resulting from penicillin. Ann. Int. Med., 28:1057, (May) 1948.
68. Kolb, L. C., and Gray, S. J.: Peripheral neuritis as a complication of penicillin therapy. J.A.M.A., 132:323, (Oct. 12) 1946.
69. Kolodny, M. H., and Denhoff, E.: Reactions to penicillin therapy. J.A.M.A., 130:1058-1061, (Apr. 20) 1946.
70. Krauel, Louis H.: Penicillin reaction. U. S. Nav. M. Bull., 46:749-750, (May) 1946.
71. Lamb, John H.: Allergic reactions from the administration of penicillin. Arch. Dermat. & Syph., 52:93-95, (Aug.) 1945.
72. Lederman, F. W.: A case of local reaction following the administration of penicillin in beeswax and oil. M. Rec., 159:540, (Sept.) 1946.
73. Leifer, W. J.: Treatment of early syphilis with penicillin. J.A.M.A., 129:1247-1251, (Dec. 29) 1945.
74. Lubowe, I. I.: Delayed reaction to penicillin treated with thephorin. N. Y. State J. Med., 48:1505, (July 1) 1948.
75. Lyons, C.: Penicillin therapy of surgical infections in U. S. Army. J.A.M.A., 123:1007-18, (Dec.) 1943.
76. Macey, Harry B., and Hays, Thomas G.: Allergic reactions to penicillin therapy. U. S. Nav. M. Bull., 45:1143-1146, (Dec.) 1945.
77. Macht, David I.: Thromboplastic properties of penicillin and streptomycin. Science, 105: 313-314, (Mar. 21) 1947.
78. MacGregor, A.: Penicillin pastilles. Brit. M. J., 1:197, (Feb. 1) 1947.
79. MacInnis, Katherine B.: Allergic reactions from handling penicillin. Ann. Allergy, 5:102-104, (March-April) 1947.
80. Mandel, E. E., Basch, F. P., and Greengard, J.: Delayed reaction to penicillin in beeswax and peanut oil (P.O.B.) in a child. Arch. Pediat., 65:119, (March) 1948.
81. Marcovicci, E. E.: Thrush as sequel to penicillin treatment. New York State J. Med., 46:1361, (June 15) 1946.
82. Markson, L. S.: Dermatitis venenata following use of penicillin ointment. Arch. Dermat. & Syph., 52:384, (Nov.- Dec.) 1945.
83. Meara, R. H.: Skin sensitivity to penicillin preparations. Brit. J. Dermat., 60:14-17, (Jan.) 1948.
84. Mendell, T. H., and Prose, P. H.: Severe allergic reactions to penicillin. Am. J. M. Sc., 212:541, (Nov.) 1946.
85. Mitchell, W., Pordy, L., and Wallach, M. B.: Occurrence of bacillus welchii gas gangrene at site of penicillin intramuscular clyses. N. Y. State J. Med., 46:61, (Jan. 1) 1946.
86. Michie, W., and Bailie, H. W. C.: A case of penicillin reaction. Brit. M. J., 1:554, (April 21) 1945.
87. Moore, J. E.: Treatment of early syphilis with penicillin. J.A.M.A., 126:67-73, (Sept. 9) 1944.
88. Morginson, William J.: The clinical use of penicillin in dermatology. South. M. J., 38: 320-326, (May) 1945.
89. Morginson, W. J.: Toxic reactions accompanying penicillin therapy. J.A.M.A., 132:915-919, (Dec. 14) 1946.
90. Morris, S. E., and Downing, J. G.: Bullous dermatitis (dermatitis medicamentosa) from penicillin. (Clin. Notes). J.A.M.A., 127:711, (March 24) 1945.
91. Mutch, M.: Penicillin black tongue and penicillin stomatitis. Brit. M. J., 1:503, (April 12) 1947.
92. Nylen, B.: Anuria in penicillin therapy. Acta Chir. Scandinav., 95:483-582, (June 25) 1947.
93. Oberst, F. W., and Murray, M.: Dermatitis from penicillin taken orally. Arch. Dermat. & Syph., 54:514-516, (Nov.) 1946.
94. O'Donovan, W. J., and Klorfajn, I.: Sensitivity to penicillin. Lancet, 2:444-446, (Sept. 28) 1946.
95. Olansky, S.: The Herxheimer reactions of relatively small doses of penicillin. J. Ven. Dis. Information, 28:26, (Feb.) 1947.
96. Peck, S. M., Siegal, S., and Bergamini, R.: Successful desensitization in penicillin sensitivity. J.A.M.A., 134:1546, (Aug. 30) 1947.

97. Perlstein, D., Liebmann, A. J., Wright, H. E., Murtaugh, J. J., and Dorrell, I.: The interference of penicillin in the determination of albumin in urine. Yale J. Biol. Med., 18: 11-13, (Oct.) 1945.
98. Penicillin lozenges. Permanente Found. M. Bull., 4:21, (1946).
99. Pillsbury, D. M.: Steiger, H. P.; and Gibson, T. E.: The management of urticaria due to penicillin. J.A.M.A., 133:1255, (April. 26) 1947.
100. Price, I. C.: Severe allergic reaction to intramuscular penicillin. Canad. M. A. J., 53:485, (Nov.) 1945.
101. Prince, Homer: Personal communication, (Jan.) 1948.
102. Pyle, H. D., and Rattner, Herbert: Contact dermatitis from penicillin. J.A.M.A., 125:903, (July 29) 1944.
103. Queries and Minor Notes: Occupational dermatitis due to penicillin. J.A.M.A., 136:730, (Mar. 6) 1948.
104. Rossellini, L. J., and Van Rooy, C. W.: Delayed allergic reaction to penicillin in oil and wax treated with procaine intravenously. Northwest Med., 45:849, (Nov.) 1946.
105. Satulsky, E. M.: Dermatitis venenata of the eyes and eyelids from the local use of penicillin. J. M. S. New Jersey, 43:95, (March) 1946.
106. Schnurman, A. G.: Five cases of latent trichophyton infection activated by the use of penicillin. Virginia M. Monthly, 73:281, (June), 1946.
107. Schultz, A.: Ocular dermatitis from local penicillin; report of two cases. Arch. Ophth., 35:145, (Feb.) 1946.
108. Scott, E. V., and Clark, E. G.: Syphilitic nephrosis as a manifestation of a renal Herxheimer reaction following penicillin therapy for early syphilis. Am. J. Syph., Gonor. & Ven. Dis., 30:463, (Sept.) 1946.
109. Scott, R. A., Murray and Turnball, J. N.: Allergic reactions to penicillin, (Letters). Brit. M. J., 1:110-111, (Jan. 18) 1947.
110. Segal, M. S., and Ryder, C. M.: Penicillin inhalation therapy. New England M. J., 236:132, (Jan. 23) 1947.
111. Selinger, Elias.: Dermatitis of the lids from penicillin eye drops. J.A.M.A., 128:437, (June 9) 1945.
112. Service, W. C.: The treatment of penicillin urticaria with nicotinic acid. Ann. Allergy, 4:397-398, (Sept.-Oct.) 1946.
113. Shaffer, J. Ordie: Generalized exfoliative dermatitis due to penicillin. New England J. M., 238:660-661, (May 6) 1948.
114. Shawyer, R. A.: Allergy to penicillin. Brit. M. J., 1:547, (March 20) 1948.
115. Silvers, Seymour H.: Contact dermatitis from amorphous sodium penicillin. Arch. Dermat. & Syph., 50:328-329, (Nov.) 1944.
116. Simon, S. M.: Untoward effects of penicillin; prophylactic use in spina bifida operation. Clin. Med., 52:87, (March) 1945.
117. Spain, D. M., and Clark, T. B.: A case of agranulocytosis occurring during the course of penicillin therapy. Ann. Int. Med., 25:732, (Oct.) 1946.
118. Stokes, J. H.: Action of penicillin in syphilis. Preliminary report. J.A.M.A., 126:73-79, (Sept. 9) 1944.
119. Strakosch, E. A.: Serum sickness-like reactions from penicillin. Rocky Mountain M. J., 43:558, (July) 1946.
120. Strazza, J. A., Jr.: Delayed sensitization to penicillin similar to serum sickness. J.A.M.A., 130:1017, (Apr. 20) 1946.
121. Strickland, D. A.: Penicillin sensitivity—Angioneurotic reaction. U. S. Nav. M. Bull., 45: 768, (Oct.) 1945.
122. Sullens, W. E.: Simulating serum-sickness reaction to penicillin. U. S. Nav. Bull., 45: 752, (Oct.) 1945.
123. Sweet, L. K.: Dumonoff, Stanley E.; Dowling, H. F.; and Lepper, M. H.: Treatment of pneumococcic meningitis with penicillin. J.A.M.A., 127:263-267, (Feb. 3) 1945.
124. Switzer, John L.: Local reaction following the initial administration of penicillin in beeswax and oil; treatment with Benadryl. M. Rec., 160:357-358, (June) 1947.
125. Templeton, H. J., Lunsford, C. J., and Allington, H. V.: Cutaneous reactions to penicillin. Arch. Dermat. & Syphil., 56:325-338, (Sept.) 1947.
126. Thomas, Evan W., Landy, Simeon, and Cooner, Corinne: Reactions to penicillin therapy for syphilis. J. Invest. Dermat., 10:77-83, (Feb.) 1948.
127. Thompson, W. E.: Effects of penicillin lozenges. (Letters, Notes, etc.) Brit. M. J., 2:600, (Oct. 19) 1946.
128. Tripoli, C. J.: Penicillin in tetanus: report of toxic reactions following its use in two other cases. New Orleans M. & S. J., 98:451, (Apr.) 1946.
129. Truitt, George W.: Reactions to penicillin. Ann. Allergy, 4:196, 1946.
130. Vickers, H. R.: Contact dermatitis caused by penicillin. Lancet, 1:307, (Mar. 2) 1946.
131. Vogel, Harold R.: Reactions to penicillin. Arch. Dermat. & Syphi., 54:713-714, (Dec.) 1946.
132. Waldbott, George L.: Procaine for urticaria from penicillin. J.A.M.A., 133:1301, (Apr. 26) 1947.
133. Walker, A. E., and Johnson, H. C.: Convulsive factor in commercial penicillin. Arch. Surg., 50:69-73, (Feb.) 1945.
134. Walker, A. E., Johnson, H. C., Case, T. J., and Kollnos, J. J.: Conclusive effects of antibiotic agents on the cerebral cortex. Science, 103:116, (Jan. 25) 1946.
135. Walker, A. E., Johnson, H. C., and Kollnos, J. J.: Penicillin convulsions. The convulsive effects of penicillin applied to the cerebral cortex of monkey and man. Surg., Gynec. & Obst., 81:692, (Dec.) 1945.
136. Walley, J. F. L.: Severe reaction after penicillin. Brit. M. J., 1:150, (Jan. 24) 1948.
137. Watson, J.: Penicillin, beeswax and allergy. Brit. M. J., 1:601, (Mar. 27) 1948.
138. Welply, W. R.: Allergic response to penicillin. Brit. M. J., 2:137 (July 27) 1946.
139. Wheatley, D. P.: Rash after penicillin lozenges. Brit. M. J., 2:448, (Sept. 21) 1945.
140. Wilcox, R. R.: Use of Benadryl for penicillin urticaria. Preliminary report. Brit. M. J., 2:732, (Nov. 16) 1946.
141. Wilensky, A. O.: Fatal delayed anaphylactic shock after penicillin. J.A.M.A., 131:1384, (Aug. 17) 1946.
142. Wright, Roy B., and Rule, Robert W., Jr.: Penicillin lozenges. J. California State Dent. A. *through* J. Canad. Dent. A., 12:185-186, (Apr.) 1946.

News Items

CHICAGO SOCIETY OF ALLERGY

We are pleased to announce that at the meeting of the Chicago Society of Allergy on May 19, 1948, the following officers were elected: President, Dr. Edward G. Tatge; Vice President, Dr. Morris A. Kaplan; and Secretary-Treasurer, Dr. Theron G. Randolph.

DIVISION OF MYCOLOGY, NEW YORK ACADEMY OF MEDICINE

The Division of Mycology of the New York Academy of Sciences held its inaugural meeting on October 22, 1948. Dr. Norman Conant, Duke University, gave a lecture on "Sporotrichosis, Clinical, Epidemiological and Immunological Aspects of the Infection."

The following officers were elected: President, Dr. Frederick Reiss, New York University School of Medicine, and Secretary, Dr. Royal M. Montgomery, Polyclinic Hospital.

COURSE IN ALLERGY

The Hansel Foundation and the American Society of Opthalmologic and Otolaryngologic Allergy conducted a Course in Allergy as related to Otolaryngology, December 6 to 11, in St. Louis at the Sheraton-Coronado Hotel.

Instruction was given in office management, history taking, skin testing, microscopic study of nasal smears, pathologic specimens, and pollen grains. The preparation and dilution of extracts for treatment and skin tests was also demonstrated. The course was well attended by members of the Society as well as other nose and throat specialists.

AVAILABLE RESIDENCIES

There are two residencies available in allergy effective the first of January and the first of July. One at the Veterans Administration Hospital (Dean's Committee Hospital) at Aspinwall 15, Pennsylvania, and the other at the Medical Center University of Pittsburgh School of Medicine. Opportunities are provided for in-patient and out-patient care, training in allergy and dermatology, instructions in botany and immunology, preparation of extracts and facilities for clinical and laboratory investigation.

Address all inquiries to Leo H. Criep, M.D., May Building, Pittsburgh, Pennsylvania.

SOUTHEASTERN ALLERGY ASSOCIATION BULLETIN

The fourth annual meeting of the Southeastern Allergy Association will be held at the Washington-Duke Hotel, Durham, N. C., on Saturday and Sunday, January 22 and 23, 1949.

Plans for the program are progressing nicely. Dr. George Rockwell, president of the American College of Allergists, and Dr. Walter Winkenwerder, president of the American Academy of Allergy, are to be the guest speakers. There will be a panel on "Infectious Asthmas" headed by Dr. Oscar Swineford and a panel on "Food Allergies" headed by Dr. Hal Davison.

This year the program committee is asking for two volunteers to present papers at the afternoon session. These papers will have to be limited to 20 minutes, with 10 minute discussions. Anyone desirous of presenting a paper, please get in touch with the secretary at once.

Saturday noon there will be an informal luncheon for members. Saturday night

there will be the regular banquet, to be held at the Washington-Duke Hotel. As usual, this will be the time for all the wives to renew their acquaintances, so be certain to bring your wife.

Hotel reservations should be made directly with the hotel—and it is suggested that this be done early!

Those planning to attend are requested to write Dr. Katherine B. MacInnis, 1515 Bull St., Columbia, S. C., for particulars.

* * *

The next issue of the ANNALS OF ALLERGY will announce the first volume of "Progress Notes in Allergy." These have appeared during the past five years in the ANNALS and have been greatly in demand. This volume will have a neat binding and will be sold at a popular price.

* * *

Dr. David Ordman, F.A.C.A., of the South African Institute for Medical Research, Johannesburg, South Africa, has commenced to organize an allergy society in South Africa for the purpose of joining the International Association of Allergists, Inc.

* * *

Dr. J. H. Frazer, who has served for many years as Medical Director of the Arlington Chemical Company, Yonkers, New York, and who has been a familiar figure at the various national allergy meetings, as well as the scientific exhibits featuring allergens, has retired and is now residing at 146 West 79th Street, New York 24, New York.

* * *

Interscience Publishers, Inc., 215 Fourth Avenue, New York 3, New York, are the sole agents for the new journal, *Acta Hematologica,* published by S. Karger, Basel, Switzerland. This will be of considerable interest to hematologists in the light of the growing importance of hematology. There is an imposing array of editors and collaborators representing hematologists from all parts of the world.

* * *

Dr. W. Randolph Graham, who for many years was a partner in the Vaughan-Graham Clinic and later the Graham-Thomas Clinic, has established the Graham Allergy Clinic, 201 West Franklin Street, Richmond 20, Virginia, and is the director, limiting his practice to allergy and internal medicine. Doctor Graham will continue a training school of allergy technology and postgraduate training as fellowships and residences in allergy. Dr. William J. Kucewicz is associated with Doctor Graham.

* * *

At the inaugural meeting of the Section of Allergists of the Hungarian Medical Trade Union, Association of Physicians, was held on March 4, 1948, the following officers were elected: Chairman, K. Hajos; Vice Chairman, E. Rajka; Secretary, L. Mosonyi.

The aim of the Section of Allergists is to promote cordial relations among the Hungarian allergists and to organize scientific meetings and postgraduate courses. With the purpose of promoting international relations, the Section of Allergy has joined the International Association of Allergists.

BOOK REVIEWS

DISEASES OF THE EAR, NOSE and THROAT. By William Wallace Morrison, M.D., with a foreword by Arthur W. Proetz, M.D. 772 pages. 359 figures. Price $8.50. New York: Appleton-Century-Crofts, Inc., 1948.

The author's position as professor of otolaryngology and attending otolaryngologist, New York Polyclinic Medical School and Hospital, et cetera, makes this volume authoritative in every respect. It is an epitome of material gathered and organized for his teaching the past twenty-three years.

The first section of the book deals with such general considerations as the taking of the history, the necessary equipment for the usual physical examination, the safe use of local anesthetic drugs and vasoconstrictor medication, and local and general anesthesia. This is followed by a chapter of general information on chemotherapy with the sulfonamide drugs and the antibiotics.

In each of the following sections there is a brief review of the essential points in the surgical anatomy, followed by a full consideration of physiology of the parts concerned which is essential to restore normal function. The etiology, pathology, signs and symptoms are concisely pictured.

The illustrations have been drawn by the author and are clear, simple and accurate. The last chapter is followed by a formulary of prescriptions for medications to be used by the patients. There is an excellent chapter on the allergic diseases of the respiratory tract.

The book is up to date, is characterized by its simplicity, and is an ideal reference book for both the student and the experienced specialist.

DIRECTORY OF PHYSICIANS INTERESTED IN CLINICAL ALLERGY. Compiled by Dr. Jonathan Forman. 178 pages. Cloth binding. Price $4.00, in orders of 5. Published by the International Correspondence Society of Allergists, 1948.

This book embraces a wealth of information, including requirements for membership in the American College of Allergists, the American Academy of Allergy and the American Society of Certified Allergists. It contains an index of the allergists in the United States and those outside of the United States.

Orders should be sent in at once, since only a limited number of copies was printed. Orders should be addressed to Dr. Jonathan Forman, 956 Bryden Road, Columbus 5, Ohio.

RELIEF OF ASTHMA BY MEANS OF LOW MELTING POINT SUPPOSITORIES

(Continued from Page 674)

REFERENCES

1. American College of Allergists: 1945 Fall Instructional Course, Chicago, Illinois.
2. Barach, Alvin: Aminophyllin in asthma. J.A.M.A., 128:589 (June 23), 1945.
3. Bird, J. C.: J. Am. Pharm. A. (Scient. Ed.), 25:475, 1937.
4. Eiler, J. J.: American Pharmacology. Vol. 1. Philadelphia: J. B. Lippincott Co., 1945.
5. Fantus, B.: General Technic of Medicine. 3rd ed., p. 373. Chicago: American Medical Association, 1947.

ABSTRACT

EXPERIMENTAL STUDY OF PURPURIC MENINGOCOCCEMIA IN RELATION TO THE SHWARTZMAN PHENOMENON. B. Black-Schaffer, Arch. Path., 43:28-54, (Jan.) 1947.

Three experiments were carried out to investigate a possible relationship between the Shwartzman phenomenon and purpuric meningococcemia.

Experiment 1 served to confirm and elaborate the fact that twice-washed meningococci, both living and dead, possess potent preparatory and provocatory substances capable of producing the local Shwartzman phenomenon.

Experiment 2, by comparing the preparatory potency of eighteen meningococcic strains, demonstrated that most of the strains (five of eight) associated with purpuric meningococcemia fall into a unique and very potent group. The strains obtained in cases of nonpurpuric meningitis produced less of the preparatory factor.

In serologic group distribution the two categories of meningococci were essentially identical.

Bilateral necrosis of the adrenal glands with hemorrhage was found in two animals of Experiment 2.

Experiment 3 was designed to test the response of rabbits to meningococcemia maintained, if necessary, over a period of twenty-four hours. General cutaneous purpura was produced in a number of animals. In addition to the cutaneous lesions, one rabbit displayed marked adrenal necrosis and hemorrhage: Waterhouse-Fredrichsen syndrome.

The close relationship of the general purpura to the local Shwartzman reaction was illustrated by the simultaneous appearance of both in rabbits which, previous to their meningococcemia, had been prepared in one or two sites by intradermal inoculation of meningococci.

Many of the animals of Experiment 3 disclosed at autopsy bilateral renal cortical necrosis. Since in rabbits this lesion is recognized as characteristic of the generalized Shwartzman reaction, it is evident that washed meningococci are capable of producing not only the local but also the general phenomenon.

It is believed that the Shwartzman substance acts directly or indirectly on the interlobular arteries of the kidneys, causing marked vasoconstriction and thus initiating the sequence of events leading to bilateral renal cortical necrosis.

Duke University Medical School
Durham, North Carolina

Abstract of paper presented at the third annual meeting of the American College of Allergists, Atlantic City, N. J., June, 1947.

Correction.—Progress in Allergy: Physical Allergy in Dermatology, Stephan Epstein, M.D., F.A.C.A., Annals of Allergy, 6:617-623 (September-October), 1948.

1. Tables 1, 2 and 3 (pages 618-619): 8γ instead of 8/gm.
2. Page 622, Line 7: However, their investigations indicate that this effect is *not* due to the "antihistaminic" action.

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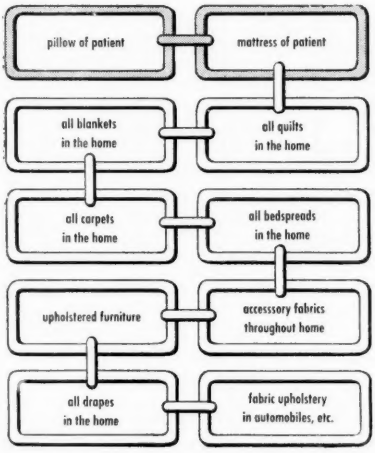

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*Arthur F. Coca, M.D., F.A.C.A. (honorary) Annals of Allergy, Oct.-Nov. 1948

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